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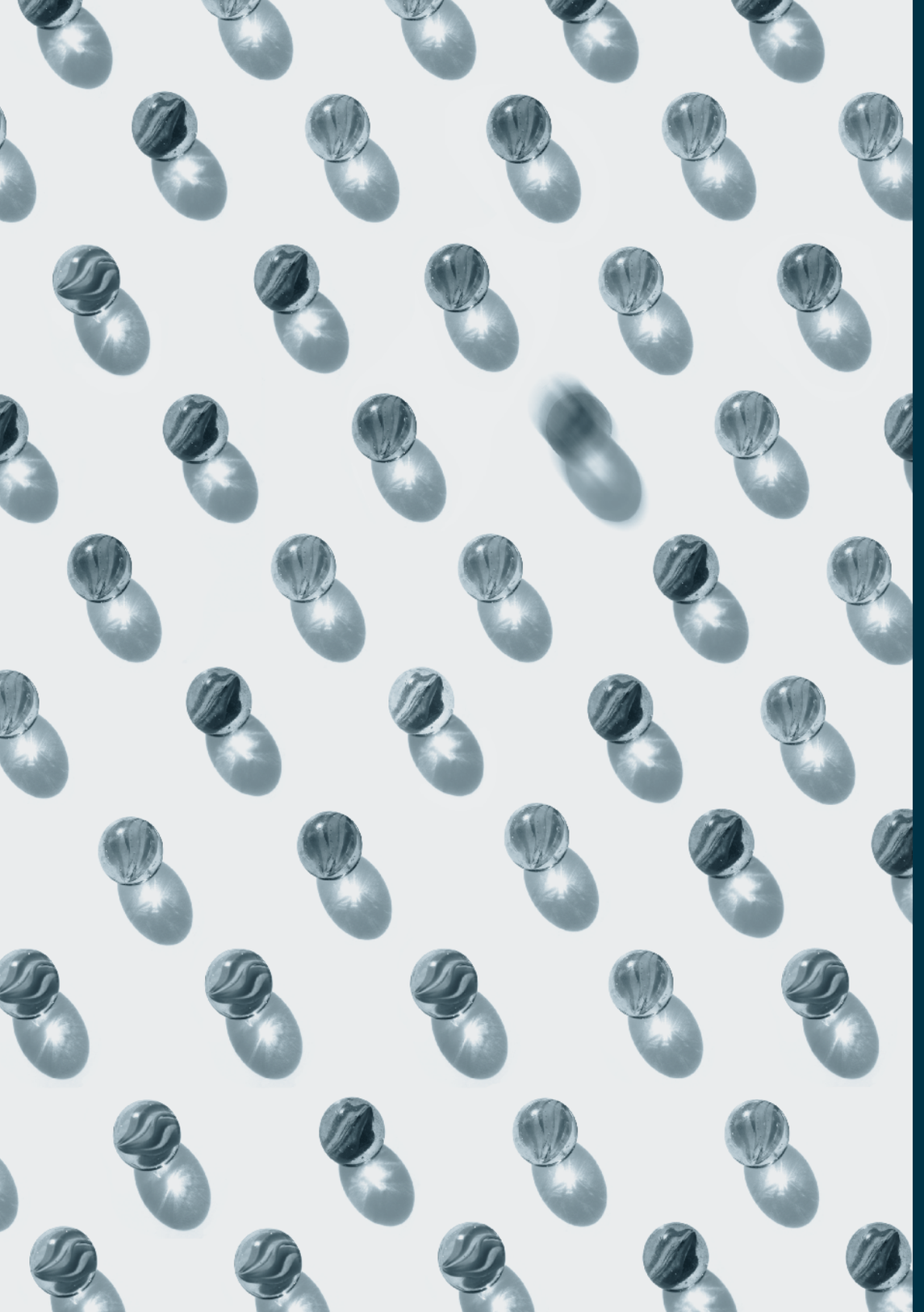

Chapter 1

Introduction: Some perspectives for improvement in prevention and treatment of gastric cancer

Ester J.M. Siemerink

Introduction

For most patients with gastric cancer cure remains elusive. Therefore better preventive, diagnostic and therapeutic options are a priority as gastric cancer remains the second leading cause of cancer related death worldwide[1], only surpassed by lung cancer.

The development of gastric cancer is considered to be an interplay of bacterial, environmental and host factors. Known risk factors for developing gastric cancer such as high salt intake, smoking and Helicobacter Pylori (H. Pylori) infection are diminishing due to lifestyle modifications. In case of H. Pylori infection however prevalence is still as high as 60% in Asia and approximately 30-40% in the Western European population[2]. Other risk factors, such as obesity and gastro-oesophageal reflux become more prevalent and change the spectrum of gastric cancers, resulting in more proximal tumours. These differences in incidence of environmental risk factors explain part of the geographic variations in gastric cancer[3].

For the following decades is has to be expected that the majority of patients, especially in the western world, still will present with an advanced stage of disease. In an attempt to improve outcome several combined treatment modalities in adjuvant and neoadjuvant setting have been applied. Although progress has been made, due to these interventions, outcome still is poor, urging the need for predictive markers to permit tailored therapy.

Therefore this review focuses on some perspectives in the prevention and treatment of gastric cancer.

Prevention

A potentially large step can be made if the data on the perspective of eradication of H. Pylori, which is still highly prevalent worldwide, live up to expectation. H. Pylori infection is considered to be acquired in early childhood. Due to migration, H. Pylori infection will become more equally distributed between currently so called low incidence (developed) and high incidence (undeveloped) countries[4].

A large database supports the concept of H. Pylori as an essential step in the development of distal gastric cancer. In essence the studies can be divided in observational studies, case control studies and eradication studies. Case control studies give increase of gastric cancer incidence around 1.8 fold[5]. Comments on this analysis usually express the opinion that this is an underestimation of the real incidence because signs of infections are missed if time between infection and diagnosis of cancer increases. A combined analysis of nested case control studies, 12 studies in over 1200 cancer patients

suggest a risk factor close to 6 for non-cardia cancer. This study also found the highest risk, 10 or more years, after infection[6]. The most impressive study is a Japanese one, after resection of (very) early cancer, 0/280 uninfected versus 36 of 1246 infected patients developed gastric cancer[7,8]. Data from nonrandomised eradication studies suggest that between 40 and 80% of cancers can be prevented[9]. A number of randomised studies have recently been reviewed and a meta-analysis has been done on those data[10]. Of these 7 studies 6 were Asian. This might influence the applicability of the conclusion to the Western situation, but there is no clear evidence that this is the case for non-cardia especially intestinal histology cancer. Over 6500 patients were randomised; in the combined control groups the cancer incidence was found to be 1.7%, in the eradication group the incidence was reduced to 1.1%. The low cancer rate explains why the individual studies did not result in significant differences. In terms of risk reduction this meta-analysis found 35% reduction, with a 95% confidence interval of 57-2%.

Clearly there does not seem to be much perspective for a definitive randomised study as sham eradication would not be acceptable. There are some side effects from antibiotic eradication, such as resistance of the target and other microbes, allergy and colitis in patients. In addition an eradication procedure leaves the possibility of re-infection. In the western population data on children indicate an incidence of 2% reinfection[11]. In the light of the obvious failure of the immunological system to clear the infection, this low percentage is amazing. Such re-infections can occur with the subtype of relative antibiotic resistant H. Pylori strains, but more often are the result of recrudescence (recolonization with the same strain)[12]. Because of side effects of antibiotics and these recurrences, the development of a vaccine, as has been done with Human Papillomavirus (HPV) seems a logical step, and might be cost-effective even in developed countries[13,14]. However progress in immunization against H. Pylori is awaiting the availability of all relevant antigens. Furthermore the site of response, the gastric mucosa and its strong acidity is not a common environment for vaccination[15].

In conclusion the available data suggest that up to 80% of distal gastric cancers are attributable to H. Pylori and therefore preventable. While in the past this would have required endoscopy it has now been established that serological detection is adequate[16]. The cost of this procedure would be minimal compared to almost all screening and intervention programs, the potential rewards would only be surpassed by results actions as asbestos elimination or changing

smoking habits, but should come close to those of HPV vaccination schemes.

Early detection

Some patient groups remain at risk for developing gastric cancer, with or without eradication of Helicobacter Pylori. Patients with chronic atrophic gastritis, a precursor lesion of intestinal type cancer, which can develop in patients with pernicious anaemia, are by some authorities advised to have endoscopic screening[17]. This is also sometimes recommended to patients after partial gastrectomy or in populations at risk such as those with familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer[18-20].
Nationwide screening in high gastric cancer incidence areas, such as northeast Asia, is assumed to be cost-effective by some[21]. Moreover the early detection of gastric cancer is considered to explain the decline of mortality by a few observational and uncontrolled trials[22-24]. However selection bias, lead and length time bias in these studies must be acknowledged. These nationwide screening programs mostly include barium x-ray, sometimes combined with H. Pylori and serum pepsinogeen testing. In case of abnormalities these tests are followed by endoscopy[25].
Endoscopy will remain the method of choice for primary diagnosis. Some improvements have been made in diagnostic optics aiming at detection of mucosal abnormalities, like chromoendoscopy, magnification narrow band imaging and confocal laser endomicroscopy[26]. New non-invasive methods to detect digestive tract carcinoma are being developed. In colorectal cancer the use of faecal occult blood test (FOBT) is common but its use is limited because of false positive results due to occult bleeding of benign sources. Further research in tumour specific changes in faeces DNA in colorectal cancer recently led to the discovery of aberrant methylation of RASSF2 and SFRP2 promotors, also in patients with gastric cancer[27]. These kind of assays are promising non-invasive techniques for early detection of cancer in the digestive tract.
The small group of patients with hereditary diffuse gastric cancers because of a germline CDH1 mutation is today more readily recognised. These CDH1 mutation carriers have a high life time risk of developing gastric cancer estimated ›80% and therefore pre-emptive total gastrectomy is often warranted. Although often not detected at screening, in most cases intramucosal foci of adenocarcinoma are found in the operation specimen and patients are curatively treated[28].

Staging

Most patients, especially in the western world, will not present with an early stage of disease. In the setting of more advanced disease the therapeutic options are either to operate or not. Local or systemic progression will prevent curative surgery. The established diagnostic modality of choice for local staging is the endoscopic ultrasound (EUS). Sensitivity and specificity for assessing serosal involvement varies between 77.8%-100% and 67.9%-100%, respectively[29]. However this technique also has limitations like inadequate staging in case of stenosis, limited penetration to access distant spread and the need to be invasive with use of sedation. Promising alternatives are multidetector row computed tomography (MDCT) using virtual gastroscopy, and parallel imaging magnetic resonance imaging (PI MRI). In a recent review the diagnostic accuracy in local staging and assessing serosal involvement was similar between EUS, MDCT and PI MRI[29]. However it is to be expected that with further improvement of MDCT and or PI MRI these techniques could overcome EUS. For the detection of distant metastasis Computed Tomography (CT) is standard. As already is the case in other cancers further improvement is expected by using Positron Emission Tomography (PET)-CT images[30]. New tracers, like 3-deoxy-3-18F-fluorothymidine (FLT) tracer might prove to be a superior combination with CT. A study by Hermann, in patients with gastric cancer (60% signet cell carcinoma) showed that compared to FDG this tracer has a higher sensitivity in detecting gastric cancer[31]. The highest accuracy to detect peritoneal involvement remains diagnostic laparoscopy as sensitivity of both CT scan and PET scan still are low[32,33].

Surgical Treatment

In selected cases, patients with tumours confined to the mucosa or superficial submucosa are amenable for minimal invasive resection techniques. Much experience with endoscopic mucosal resection (EMR) exist in the Asian world, were many people are diagnosed with early gastric cancer. More recently the en bloc curative resection rate and recurrence free rate by using endoscopic submucosal dissection (ESD), instead of EMR, was reported to be higher, at the expense of more bleeding and perforations[34]. Laparoscopic gastrectomy may cause less morbidity and is claimed to achieve acceptable oncological long term results compared to conventional surgery by some[35,36].
For the following decade however conventional surgery will remain standard of care to achieve cure in patients with gastric cancer. The five-year survival rate after curatively intended surgery still is disap-

pointingly low, 40% or less, compared to 70% or more in patients with early stage gastric cancer[37,38].
Recently an update on extensive lymph node dissection of the Dutch gastric cancer trial was published[39]. The controversy on survival benefit of extended lymphadenectomy seems closed, as results now indicated a significant survival advantage, be it at the cost of increased morbidity. Probably surgical experience is a major gateway to improvement in this respect.

Standard systemic therapy

Due to the disappointing results of surgery alone to establish cure, efforts have been made to improve outcome by adding neo- and or adjuvant chemotherapy and/or radiation therapy.
In Japan especially, adjuvant chemotherapy is routinely administrated, however results of randomized studies showed conflicting results[40,41].
New information on targeting agents however may revive this concept. Based on a large American Intergroup trial, demonstrating a significant survival benefit of adjuvant chemoradiotherapy, this strategy is currently used in the USA as standard treatment[42]. But in many other parts of the world this treatment schedule is not followed, as no survival advantage was demonstrated in patients receiving optimal surgery. In these countries, peri-operative chemotherapy based on the MAGIC trial is considered to be the preferred treatment strategy in patients with resectable gastric cancer[43]. Peri-operative chemotherapy consisted of three cycles epirubicin, cisplatin and infusional 5-fluorouracil (ECF) preoperatively and three cycles ECF postoperatively. This resulted in a five-year survival of 36% in the ECF group compared to 23% in the surgery-only group. Today this strategy is slightly converted to the epirubicin, oxaliplatin, capecitabine (EOX) regimen, after the data of the REAL-2 study showed in the metastatic setting comparable results of EOX and ECF. EOX is therefore often seen as an alternative standard outpatient peri-operative chemotherapeutic regimen without need for continuous infusion[44]. For the future it seems unlikely that changes between currently available drugs will improve results.
The standard treatment in patients with inoperable gastric cancer and a good performance is palliative chemotherapy which can increase the median overall survival with 3-6 months compared to the best support of care[45]. Accepted chemotherapeutic drugs are platinum derivates (cisplatin,oxaliplatin), fluoropyrimidines (5FU, capecitabine, S1, UFT), anthracyclines (doxorubicin, epirubicin), taxotere and irinotecan. The most common used regimen in patients with a good performance

is a combination of platinum and fluoropyrimidine derivates with epirubicin. Compared to mono chemotherapy a better response rate and a modest survival benefit are achieved, at the expensive of increased toxicity[45].

New systemic treatment options

Pre-operative treatment

In the MAGIC trial 86% of the patients completed the first preoperative 3 cycles, however only 55% of the patients started and 42% could complete the post-operative chemotherapy[43]. The FFCD 9703 trial supports the importance of the preoperative treatment as 2-3 cycles of preoperative 5- fluorouracil/cisplatin improves disease-free and overall survival in patients with resectable adenocarcinoma of gastric and lower oesophagus[46]. Therefore a logic strategy to improve the overall survival might be to optimize the preoperative chemotherapeutic regimen, but this should not result in a more toxic regimen. Based on potent chemotherapeutic drugs the most effective regimen in the metastatic setting was an ECF based regimen as is showed in the systematic review of Wagner[45]. This regimen is evaluated in the MAGIC study with a response rate combined with stable disease of ~55 %, meaning that progressive disease after 2-3 cycles will occur in ~45% of the patients and delayed surgery might affect these patients with an incomplete resection[43]. In conclusion, more active preoperative regimens are necessary. One option is the addition of preoperative radiotherapy as is shown to be active in oesophageal cancer[47]. This regimen is currently evaluated in patients with gastric cancer in a phase I/II study in our centre (Metc 2006/162). Another option to achieve a more active preoperative regimen will be the addition of new targeted agents, for example trastuzumab in patients with a Her-2 positive gastric cancer (~20% of the patients). The addition of this agent showed to be active in patients with metastatic gastric cancer with a response rate of 47%[48]. Lapatinib can target besides the Her-2 receptor the epidermal growth factor receptor (EGFR). No clinical data so far with lapatinib are available, but several phase II studies are ongoing and a phase III study with oxaliplatin/capacitabine +/- lapatinib has been initiated[49]. Bevacizumab a monoclonal antibody with a defined activity in tumours as metastatic colorectal cancer and breast cancer also seems to be an attractive new agent in patients with gastric cancer. In the perioperative setting ECF +/- bevacizumab is evaluated in a phase II/III setting. However until now the phase III study (AVAGAST) did not demonstrate an increased disease free survival when adding bevacizumab to capecitabine or 5-FU and

cisplatin in patients with inoperable gastric cancer[50].
Cetuximab, an antibody directed against the EGFR receptor demonstrated to be effective in head and neck cancer and colorectal cancer. In colorectal cancer this antibody is clinically effective in 50 percent of the tumours with a wild-type K-ras. Almost all patients with gastric cancer posses a wild-type K-ras. A phase II study in combination with standard chemotherapy in patients with advanced gastric cancer in 46 patients showed a response rate of 65% (95% Convidence Interval (CI), 50–79%) including four complete responses[51]. Based on these promising findings, phase III clinical trials have been initiated in patients with advanced gastric cancer.

Post-operative treatment

To improve the post-operative setting, an adjuvant treatment should be relatively non-toxic, to enable start probably within 6 weeks after surgery, as in many tumour types a delayed adjuvant treatment showed to be less effective[52]. Many randomized trials, with and without adjuvant combination chemotherapy, in patients with resected gastric cancer did not give an unambiguous answer in its effect on survival. The trials performed in Asia are mainly positive and the trials performed in others countries grossly showed no effect on survival[40,53]. Some factors responsible for these finding are the relative small studies, and the fact that in many trials the planned dose could postoperatively not be administrated. Based on this last mentioned item relative non-toxic effective regimens are needed to improve the adjuvant treatment. In this context trastuzumab as a targeted drug might be interesting as this showed to be effective in the metastastic setting in patients with Her2 positive tumours and already proved to prolong survival as adjuvant treatment in patients with breast cancer[48]. Another promising approach is to start with 3 courses of ECF followed by surgery and adding relative non-toxic new targeted drugs in the adjuvant setting. This strategy is currently applied in a study with preoperative oxaliplatin/5FU/erlotinib and radiotherapy followed by surgery and adjuvant erlotinib[54].

Future perspectives toward selection of patients for (specific) systemic therapy by molecular paradigms

Compared to other common tumours such as colon cancer or breast cancer, chemotherapy effects on gastric cancer are limited. This can be illustrated by using common systems of analysis of risk of death or disease progression for these tumours, and the reduction of these risks due to chemotherapy (www.adjuvantonline.com, www.mskcc.org).

Adjuvant chemotherapy for a 3 cm tumour in the breast with 3 positive lymph nodes leads to a reduction of the risk of death of approximately 30% and of relapse of 40%. In colon cancer this reduction is 50% respectively 60%. However the risk reduction of neo-adjuvant chemotherapy in gastric cancer is only 13% for death and 28% for relapse[43]. Adjuvant treatment has even lower effects. As a consequence adjuvant treatment for gastric cancer is limited to the pre operative setting while it is standard practise in the post operative setting of treatment of early colon or breast cancer.
Probably these data mean that only certain cell types in gastric cancer are sensitive to chemotherapy. It would save numerous events of toxicity if a selection could be made of patients who would be likely to benefit from treatment based on sensitivity for chemotherapy. Predictive testing has long been a holy grail in medical oncology. Although cell growth systems exposed to chemotherapy, like the Salmon assay[55], had some merits in predicting failure of treatment, these systems never have had an impact on clinical practise. There has been a long history of research into prediction of tumour response by analysis of cellular markers considered to be related to the action of chemotherapeutic drugs. The impact of finding such markers would be considerable, at first they could be used to deselect patients for toxic interventions, but the perspective of finding active drugs or combinations is alluring.
In gastric cancer a wide spectrum of drugs is used, leading to countless combinations of which no superior regimen has emerged.
A common final pathway of cancer cell death is apoptosis, controlled by the P53 gene product. Numerous studies have tried to relate tumour sensitivity to the amount or activity of this protein. However the real importance of the gene for particular clinical situations remains enigmatic. Recently an analysis at the level of polymorphisms suggested again that a less effective P53 protein could indeed be related to less effect of the treatment in gastric cancer[56]. In many earlier studies interpretation may be hampered by a merely quantitative analysis of the protein.
Activity of platinum derived drugs has commonly been associated with the presence of detoxifying enzymes such as the glutathione transferring proteins. This enzyme has a long history in research aimed at prediction or manipulation of response to platinum. Again recent studies incorporating polymorphism analysis suggested a relation between effect of platinum based regimens in gastric cancer and ineffective conjugation[57]. Comparable data were generated by the group of Goekkart[58]. Still the results of this new approach await

confirmation as older studies have resulted in conflicting data[59]. Doxorubicin like drugs are dependent in their effect on the presence of topoisomerase 2 (topo2), and will be hampered by overexpression of the P glycoprotein (PgP). An overexpression or amplification of topo2 were associated with a highly significant survival advantage in a study using high dose 5FU as a second line "rescue" treatment, even if it remained unclear if topoisomerase directed drugs were used in addition[60]. However other studies do not readily confirm this result[61]. In an earlier review Pommier concluded that no definitive value to topoisomerase levels as predictor could be ascribed[62]. Probably a confounding factor in all of these studies is that changes in topo2 genes are often part of a complex in changes in the Erbb2 complex, where amplification or overexpression can lead to deletion as well as overexpression of topo2. In those situations the Erbb2 status might surmount any effects of topo2 status. Related to topoisomerase expression in cancer cells is the over expression of PgP affecting drug efflux from the cell. Choi found however no relation with survival or time to progression after adjuvant chemotherapy with PgP overexpression[63].

Many protein markers or their genes have been in studied in relation to 5FU or its many derivatives. One of the most obvious candidates is dihydropyrimidine dehydrogenase (DPD) as its (relative) absence modulates the levels of active metabolites of 5FU. However DPD deficiency does not increase 5FU efficiency in coloncancer patients[64]. As DPD deficiency is not easily missed clinically, an impact in gastric cancer treatment seems unlikely. The same lack of correlation is found for another key enzyme of 5FU activity; Thymidilate Synthase (TS)[65,66]. No clear verdict is also possible concerning oratate phosphoribosyltransferase (OPRT) as most data are limited to in vitro studies, or in the case of a positive study correlated with the use of S1 particular to the Japanese situation[67].

In retrospect the studies aimed at predictors of response to chemotherapy have largely been unsuccessful. With most of the markers described above these results might be related to the usually purely quantitative analysis of the proteins involved. The studies using polymorphism analysis might give a new impulse in this field. A second problem particular in case of gastric cancer is that the effect of chemotherapy is limited and not related to a limited group of drugs. In this situation very large numbers of treatments have to be analysed to find meaningful correlations. Prediction of response in solid tumour oncology has entered a new era with the introduction of drugs that are directly aimed at effects of genetic changes in

cancer cells. The role model for these markers is the cKit mutation in gastro-intestinal stroma cell tumours. A most relevant recent development is the clinical evidence of activity of trastuzumab in Her-2/Neu overexpressing gastric cancers. Overexpression is present in 20% of gastric tumours, mainly of the intestinal type[68]. The presence of this marker was associated with a worse prognosis[69,70]. In these studies this marker is usually considered as a prognostic marker, however many patients received chemotherapy in the course of their disease. This consideration is relevant as this amplification will in the future determine the selection of patients for trastuzumab therapy.

The identification of new targets to develop new drugs is essential to improve the outcome of gastric cancer. Based on our current cellular and environmental knowledge targets can be divided at the level of: the DNA, cell cycle, epigenetically, growth signalling pathway and the cellular environment with angiogenesis and immunology. At the DNA level and cell cycle level drugs as cisplatin and taxotere are well known. A new target is PARP an enzyme called poly(ADP-ribose) polymerase-1, which helps in detection and repair of DNA strand breaks. Inhibitors of PARP showed promising efficacy in patients with BRCA breast cancer[71] and studies are currently being performed in other solid cancers as gastric cancer. At the epigenetic level an increased expression of histone deacetylase (HDAC) is found in gastric cancer[72]. Vorinostat a drug targeting HDAC is currently evaluated in gastric cancer[73]. At the growth signalling pathway many drugs are evaluated. In gastric cancer HSP90, a chaperone of many signalling pathway molecules as Her2/Neu, EGFR and IGFR1, is elevated. AUY922, a HSP90 inhibitor is evaluated in a phase II study in gastric cancer[74]. Angiogenesis as a relative new well known target in the last 10 years is evaluated in gastric cancer in more than 2000 studies (www.trial.gov). A less known target in gastric cancer is the immunological environment. Due to H. Pylori this can be impaired, as Anderson in 2006 showed that CTLA-4 engagement induces and maintains functional inactivation of H. Pylori-specific T cells[75]. Therefore antibodies as ipilimumab inhibiting the inhibiting effect of CTLA4 might be effective in gastric cancer. Promising results with CTLA-4 inhibition in patients with metastatic melanoma were recently published[76]. Studies in gastric cancer blocking the CTLA4 are ongoing.

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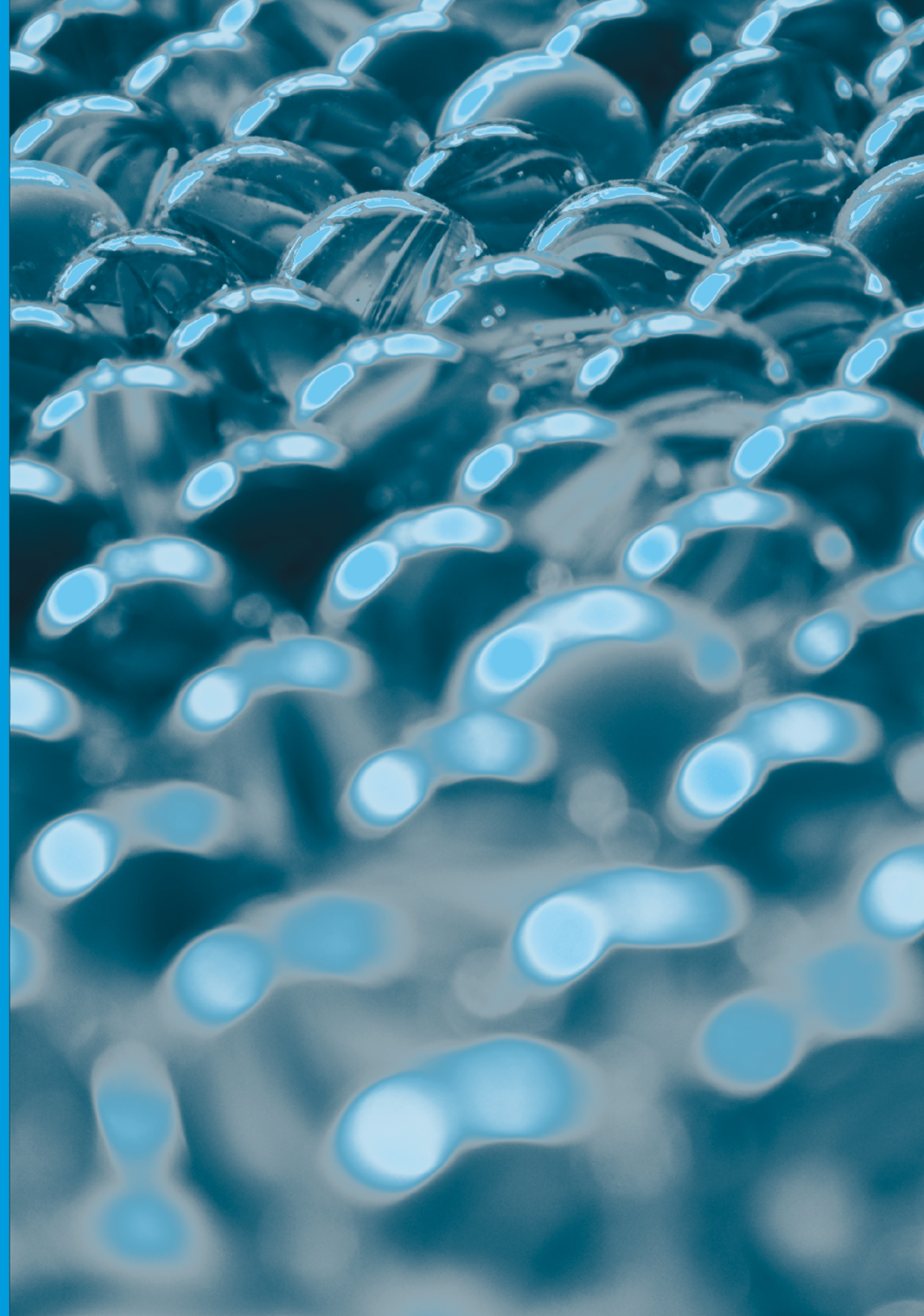

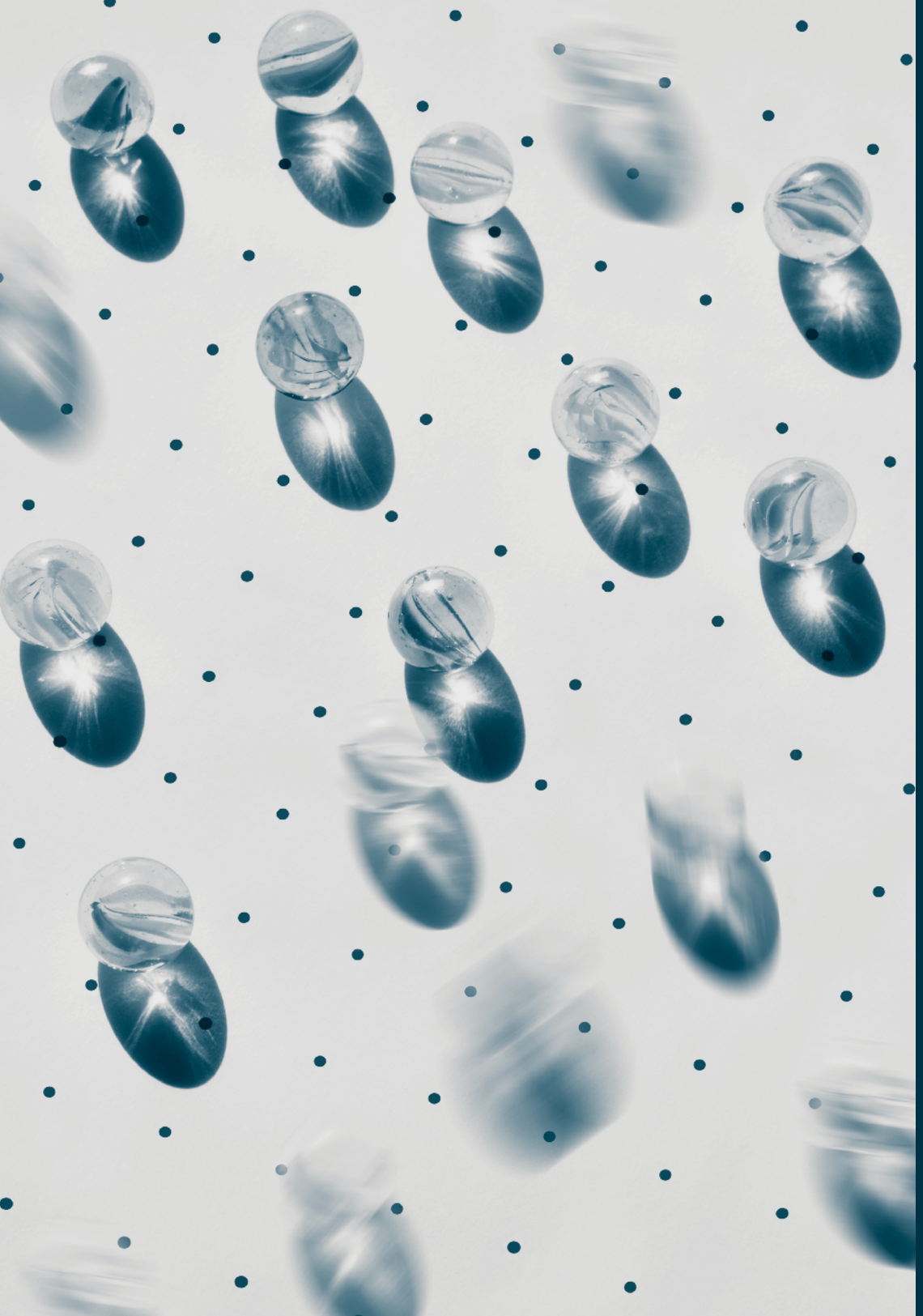

CHAPTER 2

Hereditary diffuse gastric cancer in *CDH1* mutation carriers: clinical variations and implications for counseling

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Abstract

Background and aims: *CDH1* mutation carriers have a strongly increased risk of developing gastric cancer (GC) and lobular breast cancer (LBC). **Methods:** Clinical data of GC cases and surgical and histological data of prophylactic gastrectomies and mastectomies of all 10 Dutch *CDH1* mutation families were collected. **Results:** Ten different *CDH1* mutations were found. The pedigrees comprised 36 GC cases mean age 40 years (range 20-72 years), and 1 LBC case. Twenty-nine/37 carriers alive, aged 18-61 years, underwent prophylactic gastrectomy. Invasive GC-foci and premalignant abnormalities were detected in 2 and 25 patients, respectively. In 4 patients GC/Signet Ring Cells (SRC)-foci were diagnosed at preoperative gastroscopy. Longstanding presence of SRCs without progression to invasive carcinoma was shown in 2 others. Multifocal LBC/LCIS was found in the two prophylactic mastectomy specimens. Clefts of lip and/or palate (CL/P) were reported in 7 individuals from 3 families. **Conclusions:** The age at onset and aggressiveness of GC is highly variable, which has to be included in counselling on planning prophylactic gastrectomies. The incidence of LBC is expected to increase and prophylactic mastectomy needs to be considered. The relationship between CL/P and *CDH1* needs further study to inform future parents from hereditary diffuse gastric cancer (HDGC) families adequately.

Introduction

While the incidence of gastric cancer (GC) has declined during the last decades, it remains the second cause of cancer related death worldwide[1]. In contrast to the intestinal type of GC (IGC), diffuse GC (DGC) has no clear defined risk factors and its incidence has been stable[2], suggesting that genetic factors play a more dominant role in DGC.

The far majority of DGCs is characterized by loss of expression of E-cadherin. E-cadherin is a key cell surface protein involved in inter-cellular connection and maintenance of epithelial integrity and is encoded by the tumor suppressor gene *CDH1*[3,4]. DGCs have a greater tendency to diffusely invade the gastric wall and often present at an advanced stage.

A minority of DGCs (1-3%) is seen in families with autosomal dominant GC susceptibility[5]. Germline E-cadherin inactivating mutations in the *CDH1* gene are responsible for the development of DGC in approximately 30% of families with the hereditary diffuse gastric cancer syndrome (HDGC). Diagnostic criteria for HDGC are formulated by the International Gastric Cancer Linkage Consortium[6]. Germline *CDH1* mutations have first been described in 1998 by Guilford et al. in 3 Maori kindreds with multiple DGCs at very young age[7]. Subsequently different germline mutations have been identified in families with different ethnic backgrounds worldwide[8-12]. The lifetime risk (LTR) for GC in HDGC kindreds is high and is estimated ›80%[13]. Because of this high risk and the restricted value of current surveillance modalities, prophylactic gastrectomy is recommended as the treatment of choice in *CDH1* mutation carriers in preventing advanced GC. In almost all resected stomachs of asymptomatic *CDH1* mutation carriers multiple foci of signet ring cells (SRCs) were found[14-16]. Female carriers are known to have an additional high risk of developing lobular breast cancer (LBC) with LTR of 60% by the age of 80 years, rising from age 40[6,13,17-20], whereas other tumor sites like colon and prostate might also be associated with HDGC[21,22].

In the Netherlands, *CDH1* mutation analysis is available in a clinical setting since 1998. We report on the geno-/phenotypical data of all, in total 10, Dutch families with different pathogenic germline mutations in the *CDH1* gene and summarize the pathological findings after prophylactic gastrectomy and prophylactic mastectomy in mutation carriers in these families. We also discuss the issue of counseling on associated malignancies and prophylactic options and our finding of cleft lip with/without palate (CL/P) in a subset of patients.

Methods

Individuals from families with multiple GCs and/or GC at young age were referred to our clinical genetics centers. Family details were obtained and led to the suspicion of HDGC in a subset of families. In index cases from these families mutation analysis of the *CDH1* gene was performed by PCR amplification of all coding exons including intron/exon boundaries, followed by direct sequencing using the bigdye terminator v1.1 cycle sequencing kit (PE Biosystems, Foster City, CA) and by MLPA analysis using the P08MLPA kit (MRC-Holland, Amsterdam, The Netherlands) in one laboratory.

In families with confirmed HDGC by detection of pathogenic *CDH1* mutations, relatives of index patients were counseled on HDGC and were offered presymptomatic DNA-analysis.

Based on current knowledge asymptomatic mutation carriers were advised to undergo a prophylactic gastrectomy. A Swiss roll technique was used to study the complete mucosa of the gastrectomy specimens and all abnormalities were mapped[23]. (Figure 1a and 1b) Complete clinical data of all proven/supposed mutation carriers in these families were collected and histological specimens of therapeutic and prophylactic gastrectomy specimens were reviewed by expert pathologists.

Specifically alterations as decribed in the context of *CDH1* mutation carriers were recorded; the presence of invasive carcinoma defined as infiltration in the gastric wall beyond the level of the muscularis mucosae, of clusters of signet ring cells (SRCs) in the lamina propria ‹ 3mm (also designated as in situ SRC carcinoma)[13], of intraepithelial SRCs with pagetoid spread either in the surface epithelial lining or extending deeper in the gastric crypt epithelium and any additional mucosal changes were recorded. Furthermore, details were collected about the surgical procedures and complications of the individuals who underwent prophylactic gastrectomy.

Results

Description of the 10 CDH1 mutation families

In family A, 2 cousins died of GC at ages 23 and 34 years, while their parents were healthy at that time at an age ›60 years. Several distant relatives had died of GC at a mean young age. After a pathogenic *CDH1* mutation was found in this family, 11/32 tested relatives were identified as mutation carriers of whom 9 underwent a prophylactic gastrectomy. Three mutation carriers in this family were born with a cleft lip and palate, an isolated cleft palate and a subtle lip defect (forme fruste of cleft lip) respectively.

In family B, a *CDH1* mutation was found after GC occurred in 4 family members at ages between 43 to 56 years. Subsequently, 16/25 relatives tested positive for this mutation, of whom 14 underwent a prophylactic gastrectomy.

A female patient in family C died of GC at age 27, while her father and 2 of his second degree relatives died of GC at ages between 50 and 60 years. Two sisters were shown to be carrier of a *CDH1* mutation and underwent prophylactic gastrectomy. One of them was diagnosed with T2N0M0 DGC and has no evidence of disease 7 years after surgery. CL/P was reported in 3 members of this family.

DGC was diagnosed in 2 sisters in family D from Turkish descent, at ages 37 and 39 years. Lung cancer and laryngeal cancer were reported in their father and his brother, both at age 60. The *CDH1* mutation detected in DNA of the index patients was also found in 2 children of one of them. Prophylactic gastrectomy is still under consideration.

In family E, a 42-years old man was diagnosed with GC after testing positive for a *CDH1* mutation and, despite gastrectomy and chemotherapy, he died 19 months after initial diagnosis. DNA analysis was performed because of his family history with a sister, mother and grandmother dead of GC at ages 26, 43 and 37 years. His 68 years old and asymptomatic maternal uncle was tested positive for the *CDH1* mutation.

A mother and daughter and a distant relative in family F died of GC at ages 35, 41 and 72 years. After her diagnosis of LBC at age 44, a second daughter was shown to be carrier of a *CDH1* mutation, which was also found in a third healthy daughter. Both underwent prophylactic gastrectomy, combined with prophylactic mastectomy (contralateral/bilateral). A 20-years old granddaughter proved to be a mutation carrier and gave birth to a son with a CLP. The boy's parents recently requested counseling on pre-implantation genetic diagnosis (PGD) of the *CDH1* mutation for future pregnancies.

A 40-years old female member of the Creole family G finally agreed to the proposal of a prophylactic gastrectomy 10 years after the finding of SRC-foci in her stomach. Gastric surveillance had been performed because of her family history with 1 brother and 2 sisters dead from GC at ages 32, 22 and 21. Revised histological examination of gastric biopsies taken 7 years before in her niece (daughter of her

deceased brother) showed presence of SRC-foci in these biopsies. This niece underwent a prophylactic gastrectomy at age 23. Both gastrectomy specimens showed multiple SRC-foci in the lamina propria, but no invasive carcinoma. Both patients were shown to be carrier of a *CDH1* missense mutation, which has recently proved to be a pathogenic mutation. Both parents of our first index patient died at ages ›80 years without a history of malignancies.

In family H, a 41 years old female was shown to have a *CDH1* mutation after her diagnosis of metastasized GC. Her father died of GC at age 28. Thus far, her 21 years old daughter and a 39 years old sister tested positive for the *CDH1* mutation.

In family I, a *CDH1* mutation was found in a 55-years old man of Hindustan origin, who was recently diagnosed with DGC. One half-sister was treated for DGC, 2 years before at age 36. A second half-sister and the son of a half-brother died of DGC at age 20 and 26 respectively. Their 75-years old mother, who turned out to be mutation carrier, was never diagnosed with cancer. The *CDH1* mutation was also found in the index patient's affected half-sister alive and in a second healthy, 50-years old half-sister. One first and one second degree relative of his mother were reported to have had BC and her 3 brothers died before age 50 of a 'disease in the belly accompanied by vomiting blood'.

A pathogenic *CDH1* mutation was established in DNA of a 27-years old man with DGC in family J. His both parents were alive without a history of malignancies at ages 72 and 55 and cancer was not reported in their siblings. One distant relative was treated for testicular cancer at age 40 and died of GC at age 82. At this moment, no relatives have been tested for the *CDH1* mutation.

Genotypic/phenotypic data of the 10 CDH1 mutation families

Ten different, of which 5 newly described, *CDH1* mutations were detected. Details of the functional arrays of the c.1748T›G missense mutation will be published in a series of functional studies elsewhere. GC occurred in 36 patients (M/F: 13/23). Mean age at diagnosis was 40 years (range 20-72 yrs), with 27 GCs diagnosed before the age of 50 years and 10 of them before 30 years of age. Twenty-four of 26 confirmed GCs were classified as DGC, 2 of them had clear features of an intestinal/mucinous GC. In 19 cases, including the IGCs, SRCs were reported.

Other malignancies than GC are listed in table 1. CL/P was reported in 7 individuals, of which 4 mutation carriers and 3 untested with ≤ 50% risk (Table 1).

DNA testing and follow-up of mutation carriers

Fifty-eight individuals are known carriers of one of the *CDH1* mutations, 50 by direct testing in blood or archival tissue specimens, 8 indirectly as derived from the pedigree. Of the 39 asymptomatic carriers alive, 29 opted for prophylactic gastrectomy at a mean age of 36 years (18-61 yrs), combined with prophylactic mastectomy in 2 cases (Table 2).

Prophylactic gastrectomies: clinical and surgical details

Prophylactic total gastrectomy, with Roux-en-Y-reconstruction, was performed by laparotomy in 23/29 and by laparoscopic procedure in 6/29 cases. Treatment related morbidity was recorded as suture leakage (n=3), in one patient complicated by mediastinitis, and bronchopneumonia (n=2), one resulting in ARDS. Four patients required secondary surgical procedures. Three patients underwent re-intervention respectively by endoscopic coagulation and laparotomic resection to complete removal of residual proximal gastric mucosa.
Hospitalization admission time varied from 5 to 26 days (mean: 11 days).

Prophylactic gastrectomies: histological findings

All slides of 28 available gastrectomy specimens were revised for this study. (Pre)malignant changes were seen in 27 of these specimens, consisting of invasive carcinoma in 2 patients, intramucosal carcinomas in 20 patients, and intra-epithelial clusters of SRCs in 1 patient. In 6 patients, only very subtle changes were seen with slightly atypical surface epithelial cells with cytoplasmic vacuoles. In 1 patient no gastric abnormalities were observed besides gastritis and intestinal metaplasia at age 42.
The presence or absence of SRCs and/or residual gastric mucosa in the resection margins was not systematically documented. (Table 3).

Prophylactic mastectomies: histological findings

Multiple foci of lobular carcinoma in situ (LCIS) and a 0.5 mm sized focus of invasive lobular carcinoma were detected in the contralateral mastectomy specimen of the patient who was treated for LBC before. Her sister's mastectomy specimens showed bilateral widespread LCIS.

Figure 1a.
Swiss roll

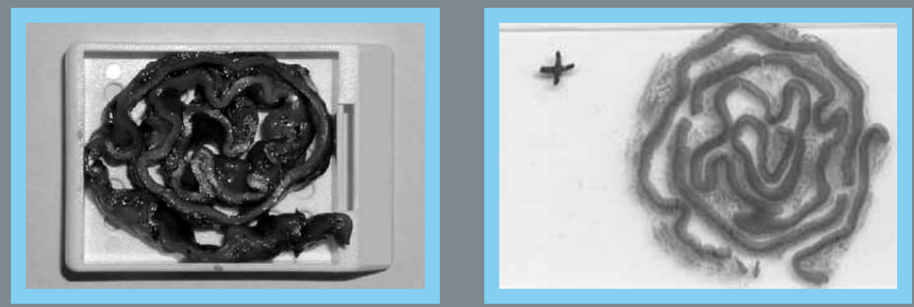
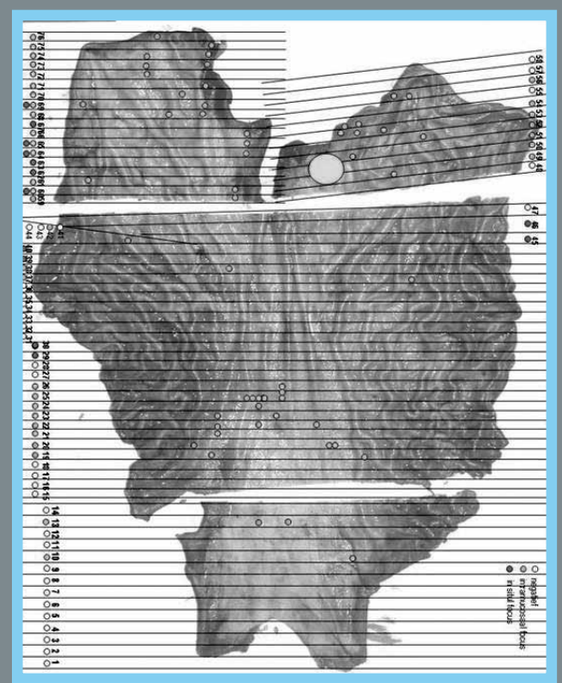


Figure 1b.
Prophylactic resected stomach with 36 SRC-foci (dots, largest spot = invasive carcinoma)



Dutch *CDH1* mutation families Chapter 2

Table 1.

Genotypic/phenotypic data of the 10 *CDH1* mutation families

fam	Mutation (prev. reported by)	exon	GC sex: n (age)	age GC (yrs)mean (range)	other tumours(age)	individuals > 18 yrs with no malignancy.		CL/P
						mut*	50% mut	
A	c.1404del (p.Ser469fs)	10	M: 3 (25,44,63) F: 6 (23,31,34,39,65,65)	43 (23-65)	GIST in duodenum (42) BC (>75)	11	4	3 (mut)
B	c.1565+2dup[24]	11	M: 1 (47)	47 (43-55)	Abd (50); PC (57)F: 3 (43,43,55) U (47) Me (43)	16	12	
C	c.1135_1137+5delins5[25]	8	M: 3 (52, 58, 58) F: 1 (27)	40 (27-52)		1	3	2(≤ 50%) 1 (mut)
D	c.2195G>A (p.Arg732Gln) Missense[8]	14	M: F: 2 (37,39)	38 (37-39)	Lu (60); La (60)	2	7	
E	c.1476_1477del (p.Arg492fs)[26]	10	M: 1 (42) F: 3 (26,37,43)	37 (26-43)		1	2	
F	c.489C>A (p.Cys163X)	4	M: F: 3 (35,41,72)	49 (35-72)	LBC (44) GIST in stomach (43)	2	4	1 (≤ 50%)
G	c.1748T>G (p.Leu583Arg) Missense	12	M: 1 (32) F: 2 (21,22)	29 (21-40)		2	9	
H	c.187C>T (p.Arg63X)[22]	3	M: 1 (28) F: 1 (41)	35 (28-41)			4	
I	c.811_812delins12 (p.Val271fs)	6	M: 2 (26,55) F: 2 (23,36)	35 (23-55)	BC (50) BC (age?)	2	13	
J	c.55_74del (p.Ser19fs)	1	M: 1 (27) F:	27				
total			36 (M/F: 13/23)	40 (20-72)	12	37*	58	7

M: male; F: female; GC: gastric cancer (symptomatic/at endoscopy/after prophylactic gastrctomy); PC: pancreatic cancer; U: uterine cancer; Me: melanoma; Lu: lung cancer; La: laryngeal cancer; BC: breast cancer; LBC: lobular breast cancer; Abd: 'cancer in the abdomen' (unspecified); CL/P: cleft lip and/or palate; mut: mutation; yrs: years

* in 27 of these patients prophylactic gastrectomy was performed, in 2 of them both gastrectomy and mastectomy.

Table 2.

DNA testing and follow-up of carriers

Fam		individuals tested for mutation*	mutation carriers*: condition at time of DNA testing		GC after mutation testing (age)	prophylactic gastrectomy	age at gastrectomy mean (yrs,range)	prophylactic mastectomy
		mut+/total	GC	asymptomati				
A	M	9/21		9		6		
	F	8/17	2	6	1 (65)	3		
		17/38				9	35 (18-49)	
B	M	7/11		7		6		
	F	11/16	1	10		8		
		18/27				14	37 (28-61)	
C	M	1/1	1					
	F	2/3		2		2**	30 (28,31)	
		3/4				2		
D	M	1/1		1				
	F	3/3	2	1				
		4/4						
E	M	2/5		2	1 (42)			
	F	1/1	1					
		3/6						
F	M	0/2						
	F	4/7	1	3		2		2
		4/9				2	44 (43,45)	
G	M	0/0						
	F	2/2		2		2**	32 (23,40)	
		2/22						
H	M	0/0						
	F	2/2	1	1				
		2/2						
I	M	1/1	1					
	F	3/3						
		4/4						
J	M	1/1						
	F	0/0						
		1/1						
total		58/97	12	46	2	29	36 (18-61)	2

* including obligate carriers and analyzed archival tissue of deceased individuals

** after detection of SRCs in endoscopic random taken gastric mucosal samples

Table 3.

Prophylactic gastrectomies: histological findings

Indiv	M/F	age	Histology	(pre)-malignant foci (n)
A1	M	49	clusters of SRCs in lamina propria	2
A2	M	46	clusters of SRCs in lamina propria	17
A3	M	45	clusters of SRCs in lamina propria	
			Helicobacter Pylori-gastritis	1
A4	M	43	clusters of SRCs in lamina propria	
			Helicobacter Pylori-gastritis	
			intestinal metaplasia	4
A5	F	42	clusters of SRCs in lamina propria	
			intestinal metaplasia/ Barrett	1
A6	M	20	clusters of SRCs in lamina propria	6
A7	M	18	clusters of SRCs in lamina propria	1
A8	F	18	clusters of SRCs in lamina propria	12
A9	F	18	clusters of SRCs in lamina propria	
			intra-epithelial SRCs	3
B1	M	61	vacuolization of surface epthelium	
			atrophic gastritis intestinal metaplasia	
			foveal hyperplasia fundic gland polyps	
			pancreatic metaplasia leiomyomas	<10
B2	M	55	clusters of SRCs in lamina propria	4
B3	F	50	clusters of SRCs in lamina propria	1
B4	M	42	chronic gastritis intestinal metaplasia	
			lymphoid aggregation	0
B5	F	40	intra-epithelial SRCs	
			vacuolization of surface epithelium	
			intestinal metaplasia	
			multiple fundic gland polyps	<10
B6	F	31	intra-epithelial SRCs	
			vacuolization of surface epithelium	
			mild gastritis areas of subepithelial edema	>30
B7	F	30	vacuolization of surface epithelium	
			fundic gland polyps	
			ectopic gastric mucosa in duodenum	<5
B8	F	31	clusters of SRCs in lamina propria	
			fundic gland polyp	1
B9	F	30	clusters of SRCs in lamina propria	
			intra-epithelial SRCs	
			vacuolization of surface epithelium	
			ectopic gastric mucosa in duodenum	6
B10	M	28	vacuolization of surface epithelium	
			fundic gland polyps	
			focal intestinal metaplasia	<5
B11	M	29	no details (surgery in hospital abroad)	?
B12	F	28	clusters of SRCs in lamina propria	7

(continuation on page 38)

Continuation Table 3.

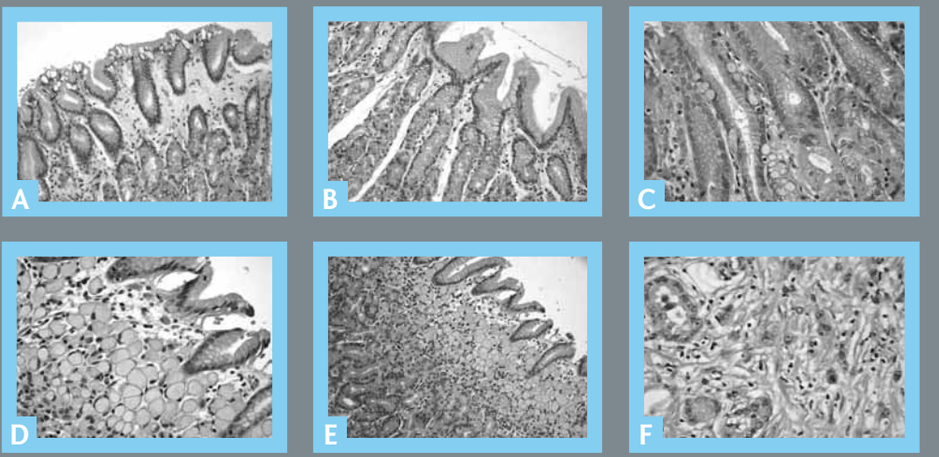
Indiv	M/F	age	Histology	(pre)-malignant foci (n)
B13	F	28	clusters of SRCs in lamina propria	5
B14	M	28	intra-epithelial SRCs	<5
C1*	F	31	invasive carcinoma	1
C2*	F	28	clusters of SRCs in lamina propria	
			parietal cell hyperplasia	5
F1	F	45	invasive carcinoma, 8 mm	
			clusters of SRCs in lamina propria	1
			vacuolization of surface epithelium	37
F2	F	43	clusters of SRCs in lamina propria	1
			intra-epithelial SRCs	10
			vacuolization of surface epithelium	1
			GIST	
			ectopic gastric mucosa in duodenum	10
G1*	F	23	clusters of SRCs in lamina propria	
			intestinal metaplasia	10
G2*	F	40	clusters of SRCs in lamina propria	
			intestinal metaplasia	
			auto-immune atrophic gastritis	
			G-cell hyperplasia	
			neuroendocrine cell hyperplasia	

Indiv: individual

* after detection of SRCs in endoscopic random taken gastric mucosal samples

Figure 2.

spectrum of putative and known *CDH1*-related alterations



A Vacuolization of the cytoplasm of surface and foveolar epithelium,
B In situ SRC carcinoma with SRC within the basal membrane replacing normal epithelial cells,
C In situ SRC carcinoma with SRC within the basal membrane replacing normal epithelial cells and showing pagetoid spread and a focus of early invasive SRC carcinoma,
D Clusters of SRCs in the mucosa, consistent with early invasive (intramucosal) carcinoma,
E Clusters of SRCs in the mucosa, consistent with early invasive (intramucosal) carcinoma,
F Invasive poorly differentiated carcinoma, infiltrating beyond the mucosa and into the submucosa and muscularis propria.

Discussion

Five *CDH1* mutations in the Dutch families were not reported previously. The other 5 mutations were previously found in more than 1 unrelated patients who were reported not to share common haplotypes, and are therefore not recognized as founder mutations[8]. The findings in all Dutch *CDH1* mutation families highlight various known and novel aspects that are important as a guideline for care in families at risk.

Phenotypic variation

Although the number of patients in this series is too small to define a genotype/phenotype correlation, some observations should be noted.

In accordance with described *CDH1* families worldwide, the majority of GC diagnoses were established before the age of 50 years[6]. However, our data showed a wide variability in age at onset (20-72 years) between, but also within families, with non-penetrance in supposed carriers at an age older than 75 years in families A, G and I. Furthermore, GC was predominantly seen in female patients (M/F: 13/23), consistent with the literature on HDGC but in contrast with SRC cases in the general population with predominance in males.

All confirmed GCs were DGCs with the exception of 2 intestinal GCs, which, however, also contained typical SRC-components. IGC or intestinal components are reported within the histological spectrum of HDGC[27]. A latent, non-proliferative, phase of SRCs has been suggested previously[28] and reasoned recently[29], and is now strongly supported by the presence of SRC 10 and 7 years prior to gastrectomy without progression to invasive cancer in 2 patients from one family. Remarkable is the variation in aggressiveness of the disease within this family. Another notable point is the finding of only subtle gastric abnormalities in 6 prophylactic treated patients and absence of typical HDGC-related histological findings in one patient, all from family B. The 6 patients showed predominantly superficial vacuolized cells without the typical morphology of SRCs, as also described by Fitzgerald et al.[13] and Carneiro et al.[30] for which the relation to *CDH1* mutation carrier status is not fully resolved. Because of the fact that these subtle lesions are the most consequent and striking feature in the gastrectomy specimens in this family and frequently the only putative *CDH1*-related alteration, it is likely that also these changes fall within the spectrum of characteristic alteration in *CDH1* mutation carriers. (Figure 2) Further study is planned to investigate if this phenotype may be characteristic for the type of mutation in this family.

In contrast to the reported excess of LBCs in some HDGC kindreds[4,6,18,20,31], we observed LBC/LCIS in only 2 patients. This is particularly unexpected because of the high BC incidence in the Netherlands (12,5%)[32], and may be explained by the fact that 18 women died of GC before the age of 50 and only a few women with a mutation or at 50% risk of being mutation carrier have reached the age of 50 years without being diagnosed with any type of cancer. The reported prevalence of LCIS in the general population ranges from 0.5% to 3.6%. In women diagnosed with LCIS, approximately 30% will develop an invasive carcinoma, most often of the ductal type. In the general population, LCIS is most likely a risk indicator for BC, but it is not itself a true precursor for invasive disease in most patients[33]. However, the presence of multiple foci of LCIS in 2 *CDH1* mutations carriers, suggest a causative relation between the presence of LCIS and the development of invasive LBC in women carrying a *CDH1* mutation.

A small number of malignancies other than GC and BC were reported. None of these cancer types are known to be related to *CDH1* mutations. Finally, the occurrence of CL/P in 7 individuals, all of Caucasian origin, in 3 of our 10 families supports the suggested association of clefts and *CDH1* by Frebourg et al.[34] They described 2 Caucasian *CDH1* mutation families with co-occurrence of CL/P and GC. In an animal model, they showed expression of *CDH1* at weeks 4-6 of embryogenesis, i.e. the critical stage of lip and palate development. However, clefts were not reported in 58 other HDGC families with a *CDH1* mutation (unpublished data, HDGC consortium Cambridge, 2008), but this may be due to reporting bias. Furthermore, in a study population of 500 individuals with nonsyndromic clefts and 500 controls, Letra et al. only observed a borderline association of CL/P with *CDH1*. No cancer data were available for this cohort[35]. Given the fact that CL/P in the general population is relatively rare (1-2/1,000 births), the CL/Ps in our cohort are considered to be related to the *CDH1* mutations, but other unknown factors must have been co-contributing to the disruption of the lip and palate closure.

Variable penetrance for GC and BC as well as variable expression of CL/P might be influenced by the nature of individual mutations, by modifying genes and by environmental risk factors[18].

Implications for clinical practice and genetic counseling

The restricted value of current surveillance modalities for *CDH1* mutation carriers was also emphasized in our study and supports the need for prophylactic gastrectomy, since most of the malignant lesions were not detected at pre-operative gastroscopy. Although

prophylactic gastrectomy is expected to be lifesaving, this procedure is not without short and long term risks. Postsurgical complications that required re-intervention were reported in 4/29 prophylactically operated patients. This number is low compared to postoperative morbidity rates of therapeutic gastrectomy. In most cases this refers to cancer treatment in mainly elder patients with co-morbidity and performed with extensive lymfadenectomy with expected higher risk for complications.[36] Long-term morbidity of prophylactic gastrectomy, such as nutritional deficiencies, food intolerance and diarrhea as well as impact on psychological functioning is seen in daily practice and deserves systematic evaluation. Moreover, long-term study in a larger patient population is needed to evaluate the oncological effectiveness of prophylactic gastrectomy. This will be largely determined by the absence of tumor cells and absence of normal gastric mucosa in the resection margins. A frozen section procedure of proximal and distal margins is warranted during operation and mentioning of this item in pathology reports is important. The Swiss roll technique is the designated pathological procedure to enable localization of lesions precisely[23]. Thus far, no recurrent disease or distant metastases were observed in our patient group.

Regarding to the LBC risk, the IGCLC does not recommend prophylactic mastectomy for all female *CDH1* mutation carriers, because of the higher mean age at onset of BC, which could justify a breast surveillance strategy[6]. Since life prognosis is expected to improve after prophylactic gastrectomy, female mutation carriers must be considered to be at high risk for developing BC after gastrectomy. Because the value of surveillance is also limited in early detection of LBC, counseling should include the option of prophylactic mastectomy. For those who choose not to perform a prophylactic mastectomy, LBC surveillance from age 35 year by annual MRI and mammography has been recommended[37].

In genetic counseling, an important issue is the preferred age to perform prophylactic procedures. Regarding gastrectomy, the youngest and mean age of occurrence of GC in the own family was the main factor in decision making in most of our patients, together with career planning. Especially young female mutation carriers have to take their possible future pregnancies into account in planning of both prophylactic gastrectomy and mastectomy, since postsurgical feeding and nutritional deficiencies could complicate pregnancies and breast feeding will not be possible. Although Kaurah et al. showed no adverse outcomes of 7 pregnancies in 4 women (of whom 3 *CDH1* mutation carriers) after gastrectomy and several studies showed no

increase of poor pregnancy outcomes after gastrectomies for reasons other than cancer, a critical attitude towards the sequence of pregnancies and prophylactic surgery is recommended[38-40].

In our opinion, there is no reason for informing future parents about the risk of CL/P in offspring as integral part of genetic counseling in all HDGC families. However, taking a family history in HDGC families should include the occurrence of CL/P in relatives. In those families positive for CL/P, current knowledge should be carefully communicated with counselees, since definite risks of CL/P are not known.

Finally, the lifelong impact of being *CDH1* mutation carrier will be, at least for a part of future parents, reason to consider the possibility of PGD and referral of these couples to specialized PGD centers may be indicated.

Conclusions

The observed wide variability of age at onset and aggressiveness of DGC and the longstanding presence of dormant SRCs in some patients has to be balanced against the limited ability of detecting early stages of GC and LBC and the impact of prophylactic surgery, in the optimal timing of genetic testing and prophylactic surgery for HDGC family members. In case of prophylactic gastrectomy, surgeons and pathologists need to be focused on complete eradication of both malignant cells and normal gastric mucosa.

Despite the observed low incidence of LBC, we recommend to discuss the option of prophylactic mastectomy with female mutation carriers, considering the expected higher incidence of LBC in the future.

The observed high incidence of CL/P supports the hypothesis that *CDH1*-mutations are involved in the disturbed lip and palate closure. This hypothesis needs to be studied in a larger patient cohort in order to inform future parents from HDGC-families adequately.

The reported complexity of counseling topics as well as surgical and pathological procedures and the expected high physical and psychosocial impact of being a mutation carrier and undergoing prophylactic interventions emphasize the need for centralized care for *CDH1* mutation carriers, provided by experts in this field working in multidisciplinary teams. Structured procedures on all aspects of this care are warranted.

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Chapter 3

Disparities in survival of stomach cancer among different socioeconomic groups in North East Netherlands

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Abstract

Background: Survival differences in stomach cancer are depended on patient, tumour and treatment factors. Some populations are more prone to develop stomach cancer, such as people with low socio-economic status (SES). The aim of this population based study was to assess whether differences in SES alone, after adjusting for confounding factors, also influence survival.

Methods: From 1989-2007 all patients with stomach cancer were selected from the cancer registry of the Comprehensive Cancer Centre North-East. Postal code at diagnosis was used to determine SES, dividing patients in three groups; low, medium and high SES. Associations between age, localization, grade, stage, and treatment were determined using Chi-square analysis. Relative survival analysis was used to estimate relative excess risk (RER) of dying according to SES.

Results: In low SES neighbourhoods diagnosis was established at older age. More distal tumours were detected in patients with low SES, whereas pathology showed more poorly differentiated tumours in patients with high SES. Overall, more resections were performed in, and more chemotherapy was administrated to patients in high SES neighbourhoods. After adjusting for confounding factors, the risk of dying was lower for patients with high SES (RER 0.89, 95% Confidence Interval 0.81-0.98) compared to patients with low SES.

Conclusion: SES proved to be an independent prognostic factor for survival in patients with stomach cancer.

Introduction

Like in most countries of the western world, mortality from stomach cancer is declining in the Netherlands: from 14.5 in 1989 to 6.7 per 100,000 person-years in 2007 (EAPC -4.1, p<0.0001).[1] The decline in mortality is related to the declining incidence (16.8 in 1989 and 9.3 in 2007, EAPC -3.3, p<0.0001), but also to some improvements in survival rates, due to better treatment options.[1] Five year survival in lower stage disease (stage IA) is 74%, which declines rapidly by increasing stage, and is 14% in stage IIIA and only 2% in stage IV disease.[1] Thus, stomach cancer remains a very lethal disease with overall five year survival rates of 21% in the period 2003-2007 in the Netherlands.[1] Stomach cancer incidence has very often been found to be inversely related to socioeconomic status (SES), with a higher incidence in the lower SES group.[2-4] The pathways through which SES influences stomach cancer risk are not established, but are likely to reflect differences in risk factors for stomach cancer: tobacco smoking, diet and infection with H. pylori.[5-7] However, on the relationship between SES and stomach cancer survival, only few studies are available.[8-10] The association between SES and survival of cancer at various sites has been examined by several epidemiologic studies and most studies found improved cancer survival by increasing SES.[10-12] Tumour characteristics as morphology and stage of disease, but also treatment have been claimed to contribute to these SES variations in cancer survival. People living in socio-economically disadvantaged areas may have poorer access to health care, which may result in delayed diagnosis and inferior treatment. However, we would not expect this to be the case in the Netherlands, as the obligatory insurance coverage should prevent inequalities in health care access. Since 1989, the cancer registry of the Comprehensive Cancer Centre North East (CCNE) collects data from all cancer patients in the North-eastern part of the Netherlands. Next to data about patient and tumour characteristics, detailed data about the treatment of cancer patients is also available. This provides us with the opportunity to study the impact of SES on the survival of stomach cancer patients in a population-based setting, taking into consideration confounding factors like age, stage and treatment.

Material and Methods

Cancer registration

All cases of stomach cancer diagnosed between 1 January 1989 and 31 December 2007 (n=9,239) in patients older than 14 years were selected from the population-based cancer registry of the CCCNE.

The CCCNE records data on all patients newly diagnosed with cancer in the north eastern part of the Netherlands, an area with 3.3 million inhabitants. The cancer registry obtains notifications from PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands. Additional sources are the national registry of hospital discharge, which accounts for up to 8% of new cases, radiotherapy institutions and haematology departments. Information on patient characteristics like gender, date of birth, date of diagnosis, primary treatment, and tumour characte-ristics such as subsite (International Classification of Diseases for Oncology (ICD-O-3))[13], histology, stage (Tumour Lymph Node Metastasis (TNM) classification)[14], and grade, are obtained routinely from the medical records approximately nine months after diagnosis.[15] The quality of the data is high, due to thorough training of the administrators and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[16] Follow-up of vital status of all patients was calculated as the time from diagnosis to death or to 1st January 2008. Death certificates are not available in an identifiable form to the cancer registry due to privacy regulations. The information on vital status was initially obtained from municipal registries and from 1995 onwards from the nationwide municipal population registries network. These registries provide virtually complete coverage of all deceased Dutch citizens.

Socioeconomic Status Scores

Postal code at time of diagnosis was used to determine SES. SES scores are available for each of the 3,876 four-digit postal code areas in the Netherlands. SES scores were available for the year 2001. The mean number of inhabitants was 4907 per postal code area in 2001. SES scores are provided by the “Sociaal Cultureel Planbureau” (a governmental organization) and based on the following items which were collected per six-digit postal code: 1) mean annual income per household, 2) the percentage of households with a low income, 3) the percentage of households with a low education.[17]

The SES scores at the six-digit postal code level were aggregated to the four-digit level. After aggregation, the variables were merged into one score by means of factor analysis (principal components analysis). A rank number (1-9) given to each postal code region was used as the SES.[16] SES was divided into three groups based on the delivered rank numbers: 1=rank number 1-5 ‘low SES’ (SES score lower than mean SES score in the Netherlands), 2=rank number 6 ‘medium SES’ (mean SES score of the Netherlands) and 3=7-9 ‘high SES’ (SES score

higher than mean SES score in the Netherlands). This SES measure is assumed to be valid for 10 years before and after the base year (2001) and is therefore applicable from 1991 to 2011.

Statistical analyses

Associations between SES of neighbourhood, age at diagnosis, gender stage of disease, localization of the tumour, histological grade of the tumour and treatment were analyzed by Chi-square analysis and calculating 95% confidence intervals (CI). Treatment was classified as resection, resection combined with chemotherapy, chemotherapy, none/unknown and 'other'. The group 'other' consists of all (combinations) of treatment procedures except the above mentioned. Relative survival was used as an estimation of disease-specific survival. It reflects survival of cancer patients, adjusted for survival in the general population with the same structure for age and gender. Relative survival is calculated as the ratio of the observed rates in cancer patients to the expected rates in the general population. Multivariable survival analyses were conducted to discriminate independent risk factors for death, expressed in Relative Excess Risk (RER). Patients with unknown stage of disease were excluded from survival analyses (n=1,732). Statistical analysis was performed with Stata version 10.

Results

In the period 1989-2007 9,239 patients were diagnosed with primary stomach cancer in the region of the CCNE. Most patients were men (66%). The mean age at diagnosis was 71 years (range 18 to 100 years). The majority of the patients were diagnosed with stage IV disease (34%). Analysis of SES revealed that patients living in neighbourhoods with lower SES levels were diagnosed on average at older age and more often with distal tumours than those living in higher SES neighbourhoods. Furthermore, patients living in neighbourhoods with the highest SES scores were diagnosed more often with a poor histological grade. For the patients living in high SES neighbourhoods the resection rate was higher as was the administration rate of chemotherapy (table 1). The median survival time was 7.5 months and the mean survival time was 27.4 months.

Table 2 shows the multivariable relative survival for patients in different SES groups. As expected, clinical and pathological factors appeared to be important prognostic factors. After adjustment for age, gender, histological grade, tumour localization, stage and type of treatment, the risk of dying was decreased independently for patients with high SES (RER 0.89, 95% CI 0.81-0.98 95%) compared to patients with low SES.

Table 1.

Distribution of individual characteristics of patients with stomach cancer in North-East Netherlands across different socioeconomic groups (%)

		Low SES		medium SES		High SES		
		%	95% CI	%	95% CI	%	95% CI	p-value*
Gender	male	64	63-66	66	65-68	67	64-70	0,117
	female	36	34-37	34	32-35	33	30-36	
Age	15-29	0.3	0.1-0.4	0.1	0.0-0.2	0.1	0.0-0.3	0.001
	30-44	2.8	2.3-3.3	2.9	2.4-3.5	3.5	2.4-4.6	
	45-59	14	13-15	16	14-17	19	17-22	
	60-74	40	38-41	40	39-42	41	38-44	
	75+	43	42-45	41	40-43	37	34-40	
Tumour localization	proximal	27	26-28	28	27-30	28	26-31	0.019
	distal	45	44-47	45	43-46	42	39-45	
	overlapping lesion	20	18-21	20	19-21	23	20-25	
	not otherwise specified	9	8-9	7	6-8	8	7-10	
Histological grade	well	3.5	3.0-4.1	3.2	2.7-3.8	3.9	2.7-5.1	0.024
	medium	20	19-21	21	20-22	19	16-21	
	poor	40	38-41	42	40-43	44	41-47	
	undifferentiated	1.0	0.7-1.3	1.4	1.0-1.7	1.7	0.9-2.4	
	unknown	36	34-37	33	31-34	32	29-35	
Stage	I	19	17-20	16	15-18	19	17-21	0.114
	II	13	12-14	14	13-15	13	11-15	
	III	15	14-16	16	15-17	17	15-20	
	IV	34	32-35	35	34-37	34	31-37	
	unknown	19	15-20	19	18-20	17	15-20	
Treatment	resection	44	43-46	46	44-47	47	43-50	0.024
	resection +chemotherapy	1.0	0.7-1.3	1.1	0.8-1.5	1.4	0.7-2.1	
	chemotherapy	4.0	3.4-4.6	4.6	4.0-5.3	5.7	4.2-7.1	
	none/unknown	38	37-40	35	33-36	34	31-37	
	other	13	12-14	14	13-15	12	10-14	

*p-values <0.05 are considered to be significant

Table 2.

Multivariable relative 5-year survival analyses for stomach cancer patients with different SES scores in the North-East Netherlands, period 1989-2007

		Multivariate	
		RER	95% CI
SES	Low	1	Reference
	Medium	0.95	0.89-1.00
	High	0.89	0.81-0.98
Age	15-29	1	Reference
	30-44	1.46	0.74-2.86
	45-59	1.54	0.80-3.00
	60-74	1.59	0.82-3.08
	75+	1.76	0.91-3.40
Gender	Men	1	Reference
	Women	0.96	0.91-1.02
Localization	proximal	1	Reference
	distal	0.98	0.92-1.05
	overlapping lesion	1.12	1.03-1.21
	not otherwise specified	1.23	1.09-1.37
Histological grade	well	1	Reference
	medium	0.88	0.74-1.05
	poor	1.10	0.93-1.30
	undifferentiated	1.37	1.04-1.81
	unknown	0.94	0.79-1.11
Stage	I	1	Reference
	II	2.16	1.92-2.43
	III	3.01	2.70-3.36
	IV	4.36	3.91-4.86
Therapy	Resection	1	Reference
	Resection+ chemotherapy	0.96	0.73-1.25
	Chemotherapy	1.56	1.37-1.77
	None/unknown	3.38	3.12-3.67
	Other	2.43	2.22-2.67

Discussion

Somewhat unexpectedly we found an association between duration of survival of stomach cancer and social economic status. This result is robust in the statistical analysis and seems convincing even if some inherent theoretical problems of data collection and analysis are considered: first we used an ecological measure of SES, which was assigned to each individual patient according to the postal code of residence at the time of diagnosis. Theoretically it is possible that individual people are misclassified and that inferences at the area level do not directly transfer to individuals. In practice, validation studies, however have found that an area-based measure of SES is a good indicator of SES for individuals.[18-20] Secondly, we could not use SES-specific life tables, because these are not available in the Netherlands. This may have resulted in an overestimation of the RER of dying for lower SES and underestimation of the RER for higher SES.[21]

Survival from stomach cancer can be expected to depend on a number of variables. Among them would be the medical intervention, yes or no, and if yes, its quality. Two kinds of intervention deserve attention in that respect. Still, the only potentially curative intervention is surgery, if it is omitted the patient will die within 6-8 months.[22] The second intervention is the use of chemotherapy in an advanced stage of disease. Although long considered to be of limited value, later studies found that a survival advantage of approximately 6 months can be the result of instituting so called palliative chemotherapy. In addition it can have real palliative value, among others in situations were the primary tumour is symptomatic.[22]

Is it conceivable that the SES advantage that we found has anything to do with treatment? At first sight it would be expected that in the Dutch society, that does not know individual financial barriers for medical care, this would be an unlikely explanation. The Dutch health care system, financially based on an obligatory insurance coverage, is designed to provide essential health care to all citizens. However a clear sign that nevertheless there are differences between different SES groups can be found in the higher resection and chemotherapy rates in high SES regions. Even so this is not necessarily by choice of the medical profession and indeed it is unlikely to be so. The most likely reason not to operate can be found in patient aspects and tumour characteristics. Patient characteristics can be summarized as “frailty” and this is correlated with age.[23] Age at diagnosis was found to be higher in the low SES group. In addition a SES gradient for the presence of co-morbidity has been observed, which could have influenced treatment decisions (Dr. M.W.J. Louwman, Erasmus

University Medical Centre Rotterdam). The other factor that gives rise to abstaining from surgery is advanced tumour growth. In our study we did not find any difference in stage between the groups. Nevertheless changes in stage can only be identified when large differences exist; delay in diagnosis will almost certainly lead to a larger tumour bulk. The older age at diagnosis may signify longer delay.
Another factor that could be of importance is the difference in health consciousness between high and low SES groups that is apparent in differences in adherence to screening procedures.[24-27] Such attitude differences could well extend into recognizing fairly common upper digestive tract complaints as requiring attention or ignoring them leading to patient delay.
Finally patient attitude could impact the use of chemotherapy in end stage disease. While surgery is a curative option, chemotherapy is palliative at that stage and prolongation of life is limited as is its quality. The choice to treat or not, will in that situation far oftener be determined by the patients attitude towards health matters, and in that respect its age.
The statistical analysis shows that not one of these factors alone is responsible for the survival advantage, but the interrelation surprisingly is strong enough to level off the advantage of distal cancer prevailing in the low SES group, and the disadvantage of high grade tumours in the high SES group.

Probably the most important observation made in this study is the possible under utilization of surgery. If this is the result of an age difference alone, recent information suggests that provided careful selection is done, successful surgery for stomach cancer is possible up to an advanced age.[28,29] Moreover, this study underscores the potential importance of preventive measures such as eradication of Helicobacter Pylori especially aimed at groups at risk such as low SES.[30]
In conclusion, SES is an independent prognostic factor for survival in patients with stomach cancer. The worse survival in low SES neighbourhoods is considered to be the result of an interrelation between patient, tumour and treatment related factors.

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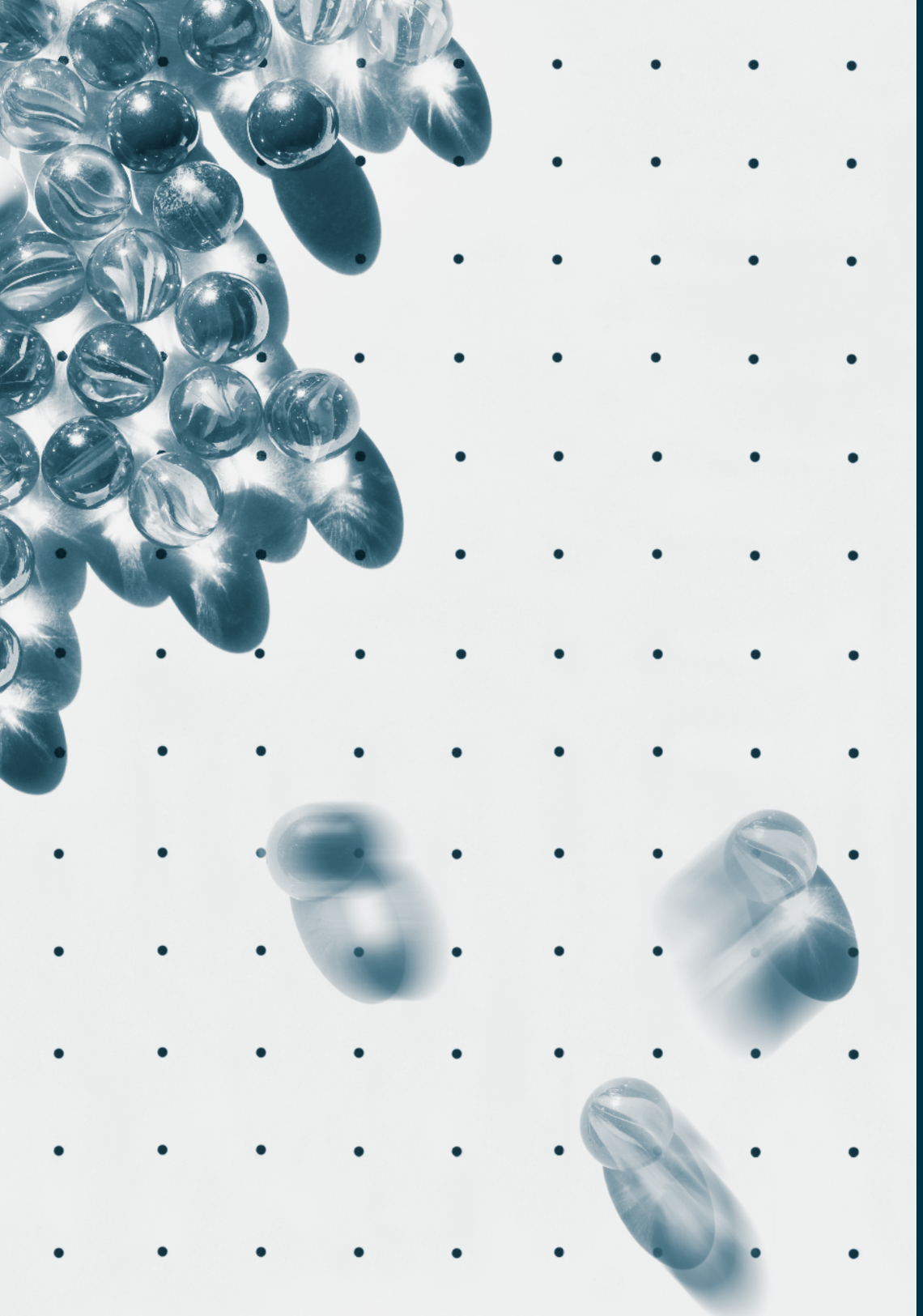

CHAPTER 4

Survival of non-western first generations immigrants with stomach cancer in North East Netherlands

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Abstract

Background: Isolated groups, like first generation non-western immigrants, are at risk for suboptimal utilisation of the health care system resulting in a worse outcome.

Methods: From 1989-2007 all patients with stomach cancer were selected from the Comprehensive Cancer Centre North-East cancer registry.

Results: After adjusting for confounding factors (patient, tumour and treatment related), the risk of dying was lower for first generation non-western immigrants (Relative Excess Risk 0.55, 95% Confidence Interval 0.43-0.70) compared to western patients.

Conclusion: The better survival of first generation non-western immigrants with stomach cancer argues against accessibility problems of the Dutch health care system.

Introduction

The Dutch health care system, financially based on an obligatory insurance coverage, is designed to provide essential health care to all citizens. However, groups that might be at risk for suboptimal care are those who are isolated; for example in a social, cultural, religious and/or communicative way[1]. A group that would fit these characteristics are first generation immigrants from non-western origin due to factors related to the migration process, such as health status, self perceived needs, health seeking behaviour, language barriers, or other cultural or religious differences, which might increase patient delay and influence outcome of care.

Accessibility of health care is particularly of interest in diseases, like stomach cancer, in which care and outcome are highly dependent on early detection. Therefore stomach cancer provides the unique opportunity of using survival as an endpoint, as delayed diagnosis and under-treatment would influence survival.

For this purpose we analysed data on survival of stomach cancer in the north east of the Netherlands for first generation non-western immigrants compared to western immigrants and autochthonic patients.

Material and Methods

Cancer registration

All cases of stomach cancer (ICD-10 code C16) diagnosed between January 1st 1989 and December 31 2007 (n=9,239) were selected from the population-based cancer registry of the Comprehensive Cancer Centre North East (CCCNE: 3.3 million inhabitants). First notifications are obtained from the nation wide network and registry of histo- and cytopathology in the Netherlands (PALGA) and the national registry of hospital discharge, radiotherapy institutions and haematology departments. Information on patient characteristics and tumour characteristics such as sub-site (International Classification of Diseases for Oncology (ICD-O-3)[2], histology, stage (Tumor Lymph Node Metastasis (TNM) classification[3]), and grade, are obtained routinely from the medical records approximately nine months after diagnosis[4]. The quality of the data is high, completeness is estimated to be at least 95%[5]. Follow-up of vital status of all patients was initially obtained from municipal registries and from 1995 onwards from the nationwide municipal population registries network and was calculated as the time from diagnosis to death or to January 1st 2008.

Registration of immigrants and autochthonic patients with stomach cancer

The cancer registry obtains country of birth from the patient files in the hospitals. When a hospital does not collect this information the country of birth is coded as 'unknown'. An unknown country of birth therefore depends on the hospital in which the patient is diagnosed and is not dependent on the patient. Of the 9,239 patients, 1,863 had an unknown country of birth and were excluded from the analyses. Of the remaining 7,376 patients, 7,259 patients were born in Europe (excluding Turkey), North America, Australia and New Zealand and were coded as western immigrants or autochthonic patient. Patients born in other countries were coded as non-western immigrants (Table 1, n=117).

Statistical analysis

Associations between country of birth, age at diagnosis, stage of disease, localisation of the tumour, histological grade of the tumour and treatment were analysed by Chi-square analysis and calculating 95% confidence intervals (CI).

Localisation of the tumour was divided in proximal (C16.0 and C16.1), distal (C16.2, C16.3, C16.4, C16.5 and C16.6), overlapping lesions (C16.8) and not otherwise specified (C16.9).

Because information on cause of death is not available in the cancer registry, relative survival was used as an estimation of disease-specific survival. It reflects survival of cancer patients, adjusted for survival in the general population with the same structure for age and gender. Relative survival is calculated as the ratio of the observed rates in cancer patients to the expected rates in the general population[6].

Multivariable five-year survival analyses were conducted to discriminate independent risk factors for death, expressed in Relative Excess Risk of dying (RER). Year of diagnosis was divided into categories and put into the multivariable model to see if there were changes in survival over time. Patients with unknown stage of disease were excluded from the survival analyses (n=1,415). Statistical analysis was performed with Stata version 10.

Results

The majority of the 7,376 patients were male (66%). The mean age at diagnosis was 71 years (range 18 to 99 years). Most patients were diagnosed in stage IV (35%). The proportion of patients from non-western origin did not change over time (data not shown).

Table 2 shows the distribution of individual patient and tumour characteristics per group. Non-western immigrants were diagnosed

Table 1.

Distribution of origin of non-western patients with stomach cancer

Country of birth	Number of patients
Africa	7
South America	2
Middle East	58
Surinam/Netherland Antilles and Aruba	18
Far East	26
Russia	6
Total	117

Table 2.

Comparison of characteristics of western immigrants and autochthonic patients with non -western patients with stomach cancer in North East Netherlands

		western immigrants and autochthonic patients		non-western immigrants		
		%	95% CI	%	95% CI	p-Value
Gender	male	66	65-67	62	53-70	0.314
	female	34	33-35	38	30-47	
Age	0-14	-	-	-	-	<0.001
	15-29	0.1	0.1-0.2	4.3	0.6-7.9	
	30-44	2.5	2.1-2.8	21	13-28	
	45-59	15	14-16	17	19-35	
	60-74	40	39-41	35	26-44	
	75+	43	42-44	13	7-19	
Tumour localisation	Proximal	29	28-30	21	14-29	0.402
	Distal	44	43-45	50	41-59	
	overlapping lesion	20	19-21	22	15-30	
	not otherwise specified	7	7-8	7	2-11	
Histological grade	poor	2.8	2.5-3.2	1.7	0.1-4.1	0.034
	medium	20	19-20	15	9-22	
	well	41	40-42	46	37-55	
	undifferentiated	0.9	0.7-1.1	3.4	0.1-6.7	
	unknown	36	35-37	33	25-4212	
Stage	I	17	16-18	15	8-21	0.125
	II	13	13-14	12	6-18	
	III	16	15-17	20	13-27	
	IV	35	34-36	42	33-51	
	unknown	19	18-20	12	6-18	
Treatment	resection	43	42-45	50	41-60	0.207
	resection +chemotherapy	1.0	0.8-1.3	1.7	0.01-4.1	
	chemotherapy	5	4.4-5.3	7	2-11	
	none/unknown	37	36-38	31	22-39	
	Other	14	13-15	10	5-16	

Table 3.

Univariate and multivariate relative 5-year survival analyses for western versus non-western patients with stomach cancer in the Netherlands, period 1989-2007

		Univariate		Multivariate	
		RER*	95% CI**	RER*	95% CI**
Country of birth	western	1	Reference	1	Reference
	non-western	0.68	0.54-0.87	0.55	0.43-0.70
Age		1.00	0.99-1.00	1.00	0.99-1.00
Gender	men	1	Reference	1	Reference
	women	0.98	0.92-1.04	0.94	0.88-1.00
Localisation	proximal	1	Reference	1	Reference
	distal	0.74	0.69-0.80	1.00	0.93-1.08
	overlapping lesion	1.26	1.16-1.37	1.23	1.13-1.34
	not otherwise specified	1.35	1.19-1.53	1.24	1.09-1.41
Histological grade	well	1	Reference	1	Reference
	medium	1.38	1.12-1.72	1.00	0.81-1.23
	poor	1.93	1.57-2.37	1.21	0.98-1.48
	undifferentiated	1.77	1.23-2.56	1.06	0.73-1.52
	unknown	2.42	1.96-2.98	1.03	0.83-1.27
Stage	I	1	Reference	1	Reference
	II	2.21	1.95-2.52	2.20	1.94-2.49
	III	3.55	3.14-4.00	3.12	2.77-3.51
	IV	9.05	8.09-10.11	4.93	4.38-5.54
Therapy	Resection	1	Reference	1	Reference
	Resection+ chemotherapy	1.58	1.22-2.03	1.29	0.99-1.67
	Chemotherapy	2.3.09	2.73-3.48	1.61	1.40-1.84
	None/unknown	6.28	5.84-6.75	3.68	3.37-4.03
	Other	4.26	3.90-4.66	2.75	2.48-3.05

*** adjusted for age, gender, localisation, histological grade, stage and treatment, ** CI= Confidence Interval**

on average at a younger age and presented more often with well differentiated tumours than western immigrants or autochthonic patients. No differences were found in localisation, stage or treatment of the tumours.

Table 3 shows the univariate five-year relative survival, as well as the multivariable five-year relative survival related to age, gender, histological grade, localisation, stage and treatment. Univariaterly, the relative five year survival for patients from western origin was 17% and 31% from non-western origin. Because year of diagnosis did not change the multivariable model, year of diagnosis was not put into the model. In general, risk of dying is slightly decreased in the multivariable analysis compared to the univariate analysis, which indicates that the risks are influenced by the other confounding factors in the table. The risk of dying is decreased independently for patients from non-western origin: RER 0.55, 0.43-0.70 95% CI. Furthermore, patients diagnosed with stage II, III or IV show an increased risk of dying compared to patients with tumours diagnosed in stage I.

Discussion

Isolated populations are at risk for experiencing access barriers to the health care system which can lead to postponing of diagnosis and worsening of outcome. Stomach cancer is a deadly disease unless early diagnosis and treatment, requiring advanced medical measures and methods, can be applied[7]. In the current study stomach cancer survival among non-western immigrants did not suggest that for them barriers in the utilisation of the health care system existed. This observation was in contrary to our expectations as especially first generation non-western immigrants are often considered as an isolated group. Not only did they not have a social network to rely on when they arrived, socially, and culturally they differed markedly from the autochthonic population. These factors have been described to contribute to isolation[8]. Especially religious convictions can lead to underrepresentation in screening programs when predestination is an issue. Also other diagnostic measures such as endoscopies and mammography's, can be debated, as are various treatment and end of life decisions[9,10]. A language barrier to some extend also can explain differences in access to healthcare and outcome of disease [11,12,13]. Finally the socioeconomic status (SES), correlated with the incidence of stomach cancer, on average is lower among non-western immigrants[14,15,16]. Moreover SES is also inversely correlated with cancer mortality[17]. Inequalities in SES explain a great amount of variability in mortality between ethnic groups especially in the USA[18,19], were people with low SES also often are uninsured.

All of these factors, especially when occurring together, could have been expected to influence the survival of stomach cancer in first generation non-western immigrants in the Netherlands adversely. On the contrary however, our results unexpectedly suggested the opposite, we observed a better outcome of patients with stomach cancer from non-western origin (RER 0,55, 0.43-0.70 95% CI) compared to those of western origin.

Differences in outcome of stomach cancer can be explained by differences in patient and tumour characteristics in addition to the functioning of the health care system. Non-western immigrants were substantially younger when diagnosed with stomach cancer than the western immigrants and autochthonic patients. We did not observe differences in tumour characteristics which could explain this difference. Patients from non-western origin, especially first generation immigrants, however are more often born in developing countries were the prevalence of Helicobacter Pylori (H. Pylori) is higher and acquired at a younger age, compared to developed countries. One could postulate that this explains part of the earlier age of diagnosis, as H. Pylori is considered a class 1 carcinogen. This however can not be the solely explanation for the difference observed. Some populations were H. Pylori is prevalent have high incidences of gastric cancer, while other highly infected populations do not. This might be attributable to differences in H. Pylori strains, next to not yet clarified genetic, dietary and environmental factors[20,21].

Although at first one would expect young age to be a favourable factor for survival (e.g. sustaining treatment) several studies have reported that stomach cancer in younger patients has a biological more aggressive behaviour[22,23]. This could result in presentation with a more advanced stage of disease and a worse outcome. However, in the multivariate analysis the outcome of the disease specific survival of stomach cancer of non-western immigrants was better also after adjusting for age and stage of disease.

Could the better outcome be explained by other more favourable tumour characteristics of non-western immigrants compared to western immigrants and autochthonic patients? We observed more proximal tumours among the western population (not significant). Proximal tumours more resemble esophageal adenocarcinoma and tend to have a more aggressive behaviour which might result in a worse outcome, compared to distal tumours[24,25]. Also non-western migrants more often had well differentiated tumours, which is a favourable tumour characteristic compared to a poorly differentiated

tumour. But again in multivariate analysis after adjusting for differentiation grade and sub localisation outcome continued to be better in the non-western patients. So no obvious patient or tumour related factors could explain the relative survival difference. Overall, patients with stomach cancer who were treated with chemotherapy alone had a worse survival compared to patients who underwent surgery. This can be explained by the fact that in most cases chemotherapy was administrated to patients with an advanced stage of disease, whereas surgery in most cases was performed with a curative intent (data not shown).

With regard to the accessibility of the health care system several favourable factors, particularly applicable to the Dutch situation of first generation non-western immigrants, could have facilitated utilisation of the medical services notwithstanding different degrees of isolation. First, the lower SES in immigrant patients would in the Netherlands not lead to financial inaccessibility of health care. Due to the obligatory insurance system in the Netherlands people from all SES are insured, in contrast to the USA were underinsurance or no insurance is a major problem in health care influencing therapy results[26]. Immigrants of this generation generally came on a contract basis and were often employed by large companies. The better survival in this group of labour immigrants might be due to the Dutch 'arbodienst', a free health service for employees within every company, which could have facilitated access to medical care largely circumventing the language barrier. Furthermore a firm social network within an otherwise heterogeneous ethnic group could compensate possible socioeconomic disadvantages of individuals or sub-groups[27]. Probably these factors; employment, insurance and cohesion alone or in combination can explain why first generation non-western immigrants did not do worse than the autochthonic population, however that they would lead to a survival advantage is unexpected and remains unexplained, especially as there is no indication that any form of treatment or intervention is applied more often in this group.

In conclusion, first generation non-western immigrants had a better survival after stomach cancer than the control population. It is suggested that accessibility of the health care system in the Netherlands was not hampered for these immigrants.

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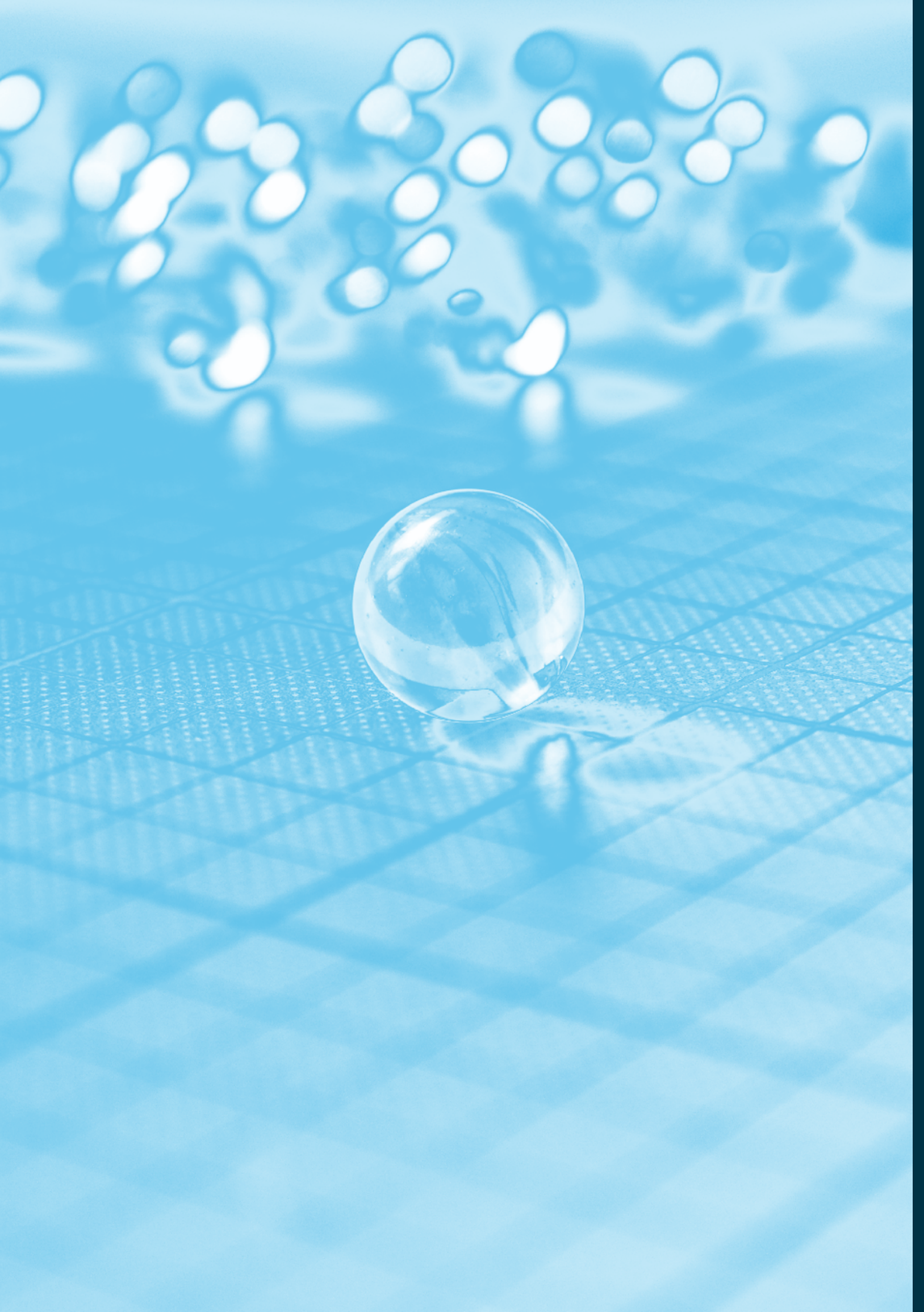

Chapter 5

Effect of hospital characteristics on outcome of patients with gastric cancer: A population based study in North East Netherlands

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Abstract

Background: Surgical resection is an important factor in the curative treatment of gastric cancer. However a variety of aspects of surgical treatment that potentially influence outcome are still not well defined. This study aims to assess the influence of hospital type, referral pattern and proximal or distal location of the tumour on the ultimate survival.

Methods: From January 1994 to January 2007, a total of 5245 patients were diagnosed with gastric adenocarcinoma in the region of the Comprehensive Cancer Centre North-East Netherlands.
Hospitals in this region were categorized into three types: teaching university (TU), teaching non-university (TNU), and non-teaching hospitals (NT). The influence of hospital type, referral for surgery and location of the tumour on the relative survival of operated patients was studied.

Results: Of the 5245 patients, 2334 patients underwent surgery. For operated patients, the 5-year relative survival was 42.5% for the TU versus 34.0% and 35.5% for respectively TNU and NT hospitals (p=0.064), with no difference (p=0.38) in relative survival (25.6-31.9%) in the proximal tumours.
A significant difference was found between the hospitals in the 5-year relative survival in the distal tumours; 59.7% in the TU versus 36.4% in the TNU and 36% in the NT (p=0.03 univariate), however this was not confirmed in the multivariate analysis (p=0.184). High referral centres did not perform better as far as survival is concerned than low referral hospitals.

In conclusion: the hospital type in our region did not significantly influence outcome of surgery for gastric cancer.

Introduction

Although decreasing in incidence, gastric cancer still is diagnosed in more than 2000 patients per year in the Netherlands. In the past decades half of them died of their disease within 5 years after diagnosis. Currently, gastric cancer ranks as the fourth cause of cancer death in the western world.[1]

It is widely recognised that prognosis depends on factors related to tumour and patient. The stage of the tumour is of paramount importance, and the patient age and especially co-morbidity are highly relevant factors in predicting outcome.[2]

More recently however, other variables, related to surgeon and even hospital characteristics have been recognised to be potentially important for the ultimate fate of the patient. These hospital related factors might be important, as the overall survival in Japan, were patients undergo more extensive curatively intended resection methods, is higher.[2]

Data demonstrating the importance of various structural characteristics including the hospital volume, surgeon volume and hospital type where the surgical intervention is performed as well as the experience and expertise of the surgical team itself, remain equivocal.[3-6]

In the population based study described here, we analysed some of these aspects in relation to the patient survival. Data were provided in a group of gastric cancer patients treated in all hospitals in the North-East region of the Netherlands regarding the hospital type and the location of the tumour, whether proximal or distal in the stomach. The outcome of this study is important in the discussion on centralization of surgical cancer care.

Patients and Methods

Patients

All patients diagnosed with primary invasive gastric cancer from January 1994, until January 2007 were selected for entry in the study by the regional cancer registry of the Comprehensive Cancer Centre North-East Netherlands.

Comprehensive Cancer Centre North-East Netherlands

This regional cancer registry is a population based registry which covers the north-eastern part of the Netherlands, a mainly rural area with a population of about 3.3 million. The area is served by 22 community hospitals, among which 8 teaching hospitals, and one university hospital, five radiotherapy departments and nine pathology laboratories. Reports of all new, cytological or histological proven cancer cases are submitted to the regional cancer registry regularly through these pathology laboratories. The national hospital discharge databank, to which hospitals in the region provide the discharge diagnosis of all admitted patients on a yearly basis, further completes case ascertainment.

Data collection

After notification, trained registry clerks abstract all relevant data directly from patient records, including pathology and surgery reports, within the hospitals. Data collection occurs at a minimum of 6 months after cytological or histological diagnosis in order to document all aspects of the primary therapy. All patients are staged according to the TNM system.[7,8]

In the Netherlands the municipal population registries contain information on the vital status of their inhabitants. Since October 1994 population data from all Dutch municipalities are collected in a national database. Vital status was established through linkage of cancer registry data with the national automated population registry.

Variable definitions and Statistics

The referral rate was calculated as the proportion of all operated patients, within the population of patients diagnosed in a given hospital, which were operated in another hospital.

Survival time was calculated from the date of diagnosis and ended at the date of death or the date of most recent linkage with the national automated populated registry, whichever came first. The 5-year overall survival rates were estimated using the actuarial method and survival was compared with the log rank test. Besides overall survival, relative survival rates were estimated. The relative survival is an estimate for the disease-specific survival and is calculated by dividing the absolute overall survival in our cohort by the expected survival based on age, sex and period matched mortality rates from the general population. The main advantage of using the relative survival is that it does not rely on cause of death information and captures both direct and indirect mortality due to gastric cancer and its treatment. Multivariate analysis of relative survival was performed according to the method described by Dickman et al.[9]

Results

Patients

In the period January 1994 until January 2007, 5245 patients were diagnosed with gastric adenocarcinoma of which 3440 were male.

The median age was 72.3 (range: 18.5-98.3) years. Patient characteristics are described in Table 1. A large proportion of the patients was diagnosed at an advanced stage, 2714 patients were in stage IIIA or higher. A further 954 patients were insufficiently staged. One hundred ninety-four patients were diagnosed in the university hospital, 2869 in the non-university teaching hospitals and the remaining 2182 patients were diagnosed in community hospitals.
As table 1 shows, 2334 patients underwent surgery. Older age (p<0.001), advanced or unknown stage (p<0.001) and proximal tumour location (p<0.001) resulted in a lower probability of tumour resection. A tumour with intermediate or poor differentiation was also associated with less surgery, but this was highly correlated with stage. In all, 40.2% of the patients diagnosed in non-teaching hospitals were operated on, compared to 45.6% and 43.5% for non-university teaching and university hospitals, respectively (p=0.162). Only a minority of the operated patients received (neo)adjuvant chemotherapy, respectively 57 out of 2334 patients.

Hospitals characteristics

A total of twenty-three hospitals participated with fourteen non-teaching hospitals, eight teaching hospitals and one university hospital. For proximal gastric cancers a difference in stage distribution was observed (p=0.039) due to a higher frequency of patients with stage III and a lower frequency of stage IV cancers among patients operated in the university hospital. For the non-proximal tumours there were no meaningful differences in stage and sub-site distribution between the three hospital types. There was some imbalance in the distribution over the age-groups (p<0.001), with slightly younger patients operated in the university hospital although overall the age distribution did not appear to differ that much when analysed categorical (Table 2).

Referral characteristics

Of all operated patients 6% were referred for surgery. Referral differed markedly by tumour sub-site, however. Of the operated patients with a tumour located in the proximal part of the stomach 18.0% were referred for surgery, while only 2.6% of the operated patients with a non-proximal tumour (body or distal part of the stomach) were referred for surgery. The non-teaching hospitals referred 10.9% of the operated patients diagnosed in their hospitals, 35.2% of the patients with proximal and 4.6% of the patients with non-proximal tumours. Of the fourteen non-teaching hospitals, seven had a high propensity

Table 1.
Characteristics of patients diagnosed with gastric adenocarcinoma between 1994-2006, all patients combined, operated and non-operated patients

		Total	Operated	Not-operated	
		N	N	N	*p-value
Gender	Men	3440	1555	1885	0.157
	Women	1805	779	1026	
Age at diagnosis	<50	364	189	175	<0.001
	50-59	672	332	340	
	60-69	1207	627	580	
	70-79	1751	835	916	
	80+	1251	351	900	
Histology	Adenocarcinoma, nos	4,051	1773	2278	<0.001
	Mucinous	282	158	124	
	Signet ring cell	767	403	364	
	No microscopic confirmation	145	0	145	
Tumour location	Cardia&fundus	1509	517	992	<0.001
	Body & curvature, nos	886	464	422	
	Antrum & pylorus	1430	888	542	
	Overlapping & unspecified	1420	465	955	
Differentiation	Good	144	99	45	<0.001
	Intermediate	1031	633	398	
	Poor	2238	1231	1007	
	Unknown	1832	371	1461	
Stage	Stage 1A	317	264	53	<0.001
	Stage 1B	562	464	98	
	Stage 2	698	603	95	
	Stage 3	807	598	209	
	Stage 4	1907	386	1521	
	Unknown/not applicable	954	19	935	
Therapy	Surgery	2277	2277	0	<0.001
	Surgery&CT	37	37	0	
	Neoadjuvant CT & surgery	20	20	0	
	CT	259	0	259	
	CT & RT	15	0	15	
	Other/none	2637	0	2637	
Total		5245	2334	2911	

* p-value based on Chi-square or Fisher's exact test where applicable

Table 2.

Stage and age distribution for operated patients according to hospital type were surgery was performed 1994-2006, stratified by tumour subsite

		Total	Teaching, university	Teaching, non-university	Non- teaching	p-value
	Stomach: cardiaGfundus	*N*	*N*	*N*	*N*	
Stage	Stage 1A	41	9	23	9	0.039*
	Stage 1B	89	13	46	30	
	Stage 2	171	22	100	49	
	Stage 3	152	35	92	25	
	Stage 4	61	7	38	16	
	Unknown	3	2	0	1	
Age	<60	163	34	99	30	0.101
	60-69	174	23	100	51	
	70+	180	31	100	49	
	Median	65.4	64.4	64.8	66.8	0.169
	(IQR#)	(57.9-72.5)	(55.8-72.1)	(57.5-72.5)	(61.5-73.0)	
Total		517	88	299	130	100.0
	Stomach: other					
Stage	Stage 1A	223	14	121	88	0.409*
	Stage 1B	375	22	192	161	
	Stage 2	432	17	248	167	
	Stage 3	446	14	254	178	
	Stage 4	325	13	181	131	
	Unknown	16	2	6	8	
Age	<60	358	23	198	137	0.391
	60-69	453	18	251	184	
	70+	1,006	41	553	412	
	Median	71.7	70.1	71.8	71.8	
	(IQR**)	(63.0-78.0)	(58.1-77.6)	(62.7-77.8)	(63.8-78.3)	<.001
Tumour location	Body&curvature, nos	464	20	252	192	0.359
	Antrum&pylorus	888	38	478	372	
	Overlapping& unspecified	465	24	272	169	
Total		1817	82	1,002	733	

* Excluding stage unknown

** IQR=Inter Quartile Range

Table 3.

Hospital type, volume and referral pattern for gastric cancer-surgery for hospitals in the North-East Netherlands between 1994 and 2006

Hospital type	Number of operated patients			
Hospital of diagnosis (n=number of hospitals; Operated number of patients/year)	**Cardia/fundus tumours**		**Body/distal tumours**	
	Operated in hospital of diagnosis	**Referral for surgery**	**Operated in hospital of diagnosis**	**Referral for surgery**
	N	**N**	**N**	**N**
Hospitals (n=7; <5 year)	42	39	278	18
Hospitals (n=7; 5-9 year)	83	29	443	17
Non-teaching	**125**	**68**	**721**	**35**
Hospitals (n=1; 5-9 year)	23	1	88	1
Hospitals (n=7; ≥10 year)	256	24	903	11
Teaching non-university	**279**	**25**	**991**	**12**
Hospital (n=1; 5-9 year)	20	0	58	0
Teaching university	**20**	**0**	**58**	**0**
Total	424	93	1,770	47

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Table 4.

Overall and relative 5-year survival and estimated excess risk of death with 95% confidence intervals (95% CI) for operated patients with gastric cancer, diagnosed between 1994-2006

	All gastric cancers					Proximal gastric cancer					Distal gastric cancer				
	Univariate		Multivariate			Univariate		Multivariate			Univariate		Multivariate		
	5-year OS	5-year RS	EMR	95% CI	*p-value	5-year OS	5-year RS	EMR	95% CI	*p-value	5-year OS	5-year RS	EMR	95% CI	*p-value
Sex					0.075					0.519					0.224
male	27.1	34.0	1.00			24.7	28.6	1.00			28.0	36.0	1.00		
female	30.9	37.4	0.90	0.79-1.02		21.4	24.3	0.91	0.68-1.22		32.1	39.1	0.92	0.80-1.06	
Age					0.055					0.206					0.050
< 60 (ref)	32.0	32.8	1.00			23.8	24.4	1.00			35.7	36.5	1.00		
60-69	31.5	35.0	1.03	0.89-1.21		28.8	31.9	0.85	0.64-1.12		32.6	36.1	1.13	0.94-1.37	
70+	25.1	36.8	1.17	1.01-1.34		20.3	27.6	1.09	0.83-1.44		25.9	38.4	1.23	1.04-1.45	
Period					0.001					0.092					0.014
1994-1999	26.7	33.8	1.00			21.3	25.2	1.00			28.1	36.1	1.00		
2000-2006	30.0	36.3	0.83	0.74-0.94		27.5	30.9	0.83	0.65-1.04		30.9	38.1	0.84	0.73-0.96	
Stage					<0.001					<0.001					<0.001
stage 1 (ref)	55.6	70.5	1.00			46.1	54.2	1.00			57.6	73.8	1.00		
stage 2	26.5	32.5	2.96	2.44-3.60		24.5	28.3	2.12	1.49-2.99		27.2	34.1	3.25	2.57-4.13	
stage 3	11.2	13.5	5.20	4.31-6.27		14.0	15.9	3.49	2.43-4.99		10.3	12.7	5.99	4.78-7.51	
stage 4	5.3	6.3	8.05	6.61-9.80		2.0	2.3	4.93	3.29-7.38		5.9	7.1	9.37	7.43-11.83	
Hospital type**					0.112					0.433					0.184
Non-teaching (ref)	28.6	35.5	1.00			27.1	31.9	1.00			28.9	36.0	1.00		
Teaching non-university	27.4	34.0	0.96	0.74-1.25		22.6	25.6	0.99	0.62-1.56		28.7	36.4	0.92	0.66-1.29	
Teaching university	34.7	42.5	0.76	0.56-1.03		24.5	29.2	0.80	0.51-1.26		47.5	59.7	0.66	0.40-1.07	
Volume hospital***					0.880					0.778					0.814
< 5 patients operated/year	28.5	34.6	1.00			30.5	35.0	1.00			27.8	34.5	1.00		
5-9 patients operated/year	28.2	35.5	1.00	0.81-1.22		23.4	28.1	1.15	0.75-1.76		29.1	37.1	0.98	0.77-1.25	
≥ 10 patients operated/year	28.4	35.2	1.06	0.80-1.40		22.5	25.9	1.14	0.73-1.78		30.1	38.3	1.08	0.74-1.55	
Referral rate hospital****					0.377					0.627					0.498
Low (< 5.0%)	28.7	34.5	1.00			24.7	28.4	1.00			29.8	37.8	1.00		
Intermediate (5.0-15.0%)	28.0	35.3	0.95	0.77-1.17		20.7	25.2	1.10	0.74-1.63		29.7	37.8	0.91	0.71-1.17	
High (> 15.0%)	26.0	32.2	1.12	0.91-1.39		23.6	27.4	1.19	0.82-1.72		26.7	33.7	1.08	0.83-1.40	

OS=Overall survival, RS=relative survival, EMR=Excess Mortality Risk, 95% CI=95% Confidence Interval

* p-values apply to the multivariate model, adjusted for time since diagnosis

** teaching status based on surgical subspecialisation

*** subdivision based on <5 versus 5-9 or ≥ 10 patients operated/ year based on all gastric cancers combined

**** subdivision based on <5%, 5-15% and >15% referral of patients for surgery based on all gastric cancers combined

to refer (referral rates 50-83%) patients with proximal gastric cancers for surgery and three hospitals rarely (0.0%-10.0%) referred patients. The eight non-university teaching hospitals referred 2.8% of the patients diagnosed in their hospitals, 8.2% of the patients with proximal and 1.2% of the patients with non-proximal tumours (Table 3).

Survival in relation to patient, tumour and hospital characteristics

The 5-year relative survival rate in the period of 1994-2006 for men with gastric cancer was 34.0% versus 37.4% for women. Age over 70 had a detrimental effect on survival compared to age ‹60 years with an excess mortality risk of 1.17 (1.01-1.34; p=0.022). The 5-year relative survival markedly decreased with more advanced stage, respectively 85.0% in stage IA, 62.0% in stage IB, 32.5% in stage II, 13.5% in stage III, 6.3% in stage IV (p<0.001). Assessing all operated gastric cancers combined; 5-year relative survival did not significantly differ by hospital type, referral pattern or volume of the centres. Although relative survival appeared to be somewhat better in the TU, as the 5-year relative survival was 42.5% for the TU versus 34.0% and 35.5% for respectively TNU and NT hospitals (p=0.064 univariate). Survival was also analysed separately for patients with proximal and non-proximal tumour. For proximal tumours outcome was strongly associated with stage, but neither hospital volume, nor teaching characteristics were significant factors. However in univariate analysis 5-year relative survival of the non-proximal tumours was significantly better in the TU compared to TNU and non-teaching hospitals (p=0.033 univariate) (Table 4). After adjusting for sex, age, period, stage, volume, referral and time since diagnosis these differences no longer reached statistical significance. Survival with respect to age, stage, volume (‹ 5, 5-9 and ≥ 10 patients/year) and referral rate (‹5%, 5-15% and›15%) was not different between the hospital types (Table 4).

Survival before and after the year 2000, for all types of gastric cancer combined did differ. For proximal cancer the results were similar between the two periods. However survival for non-proximal cancer was better in the later period. This improvement was not related to any of the hospital factors (volume teaching academic).

Discussion

In this population based study patient characteristics such as gender and age distribution are comparable to other European countries.[10] Age, subsite and histology type are known factors in explaining survival variability.[11] In our study older age, advanced or unknown stage, poorly differentiated tumours and proximal location resulted

in lower probability of resection. Moreover in gastric cancer both tumour (T) and nodal (N) status are important elements in determining treatment plans and independent prognostic factors of long-term survival.[12-14]

However factors that are neither patient nor tumour related have been reported to influence the outcome of curative intended surgery in cancer patients. Some of them are related to the experience and expertise of the surgical team and the case volume. Others stem from non-oncological surgical experience, such as expertise in extensive transplantations. Several studies demonstrated hospital and surgeon volume to have an important impact on short and long term survival in patients with potentially curative resection in different cancer types. Better outcome was also found in specialised centres.[15-18] Verhoef et al. described significantly better outcome in oesophageal cancer surgery in the university hospital compared with other, non-university teaching and non teaching, hospitals in our region.[19] As shown in oesophageal cancer, some studies also support the impact of hospital and surgeon related factors on short and long-term results in gastric cancer.[20-22]

The 5-year overall survival rate in our study reflects reported stage-specific 5-year survival rates of 10-64%.[23] Patients treated in high referral hospitals did not have a better long term survival than those treated in low referral hospitals. Survival also seemed independent of hospital type for the whole group of surgical patients. Although relative survival appeared to be somewhat better in the TU compared to TNU and NT hospitals (42.5% versus 34.0% and 35.5% of TNU and NT (p=0.064)). This could partly be explained by an imbalance in tumour and patient characteristics between the hospital types. On average less patients, with lower stages of proximal gastric cancer and slightly younger of age were operated in the TU hospital (Table 2). With regard to survival and tumour location, there were no hospital related differences in outcome in proximal gastric cancer. However overall outcome in that location was worse compared to that in the distal stomach, an observation also found in the work of others.[24-27] For distal gastric cancer the univariate analysis showed a significant difference in the 5 year relative survival regarding hospital type, in favour of the university hospital (57.7 % versus 36.4% TNU and 36% NT). This difference could not be confirmed in multivariate analysis and to some extend might be explained by patient selection; the TU hospital operated on average, younger patients. Therefore, hypothetically maybe the high volume more experienced non-university hospitals (TNU and TU) have balanced the more academic approach of the

tu resulting in no significant difference in survival. With regard to long-term survival we also did not observe hospital volume to play an important role. Of note, all surgeons in our region are low volume surgeons and the subdivision of centres based on volume of <5, 5-9, ≥ 10 patients operated/year served as a suitable separator between its 23 centres. Within this small window no striking differences were found in relation to survival. Controversy on the role of surgical volume still remains, as is also discussed by other authors.[3,5,6,28] This observation suggests that other factors than sheer number of procedures are important for outcome. As in our case, the university hospital is a low volume hospital for gastric cancer, it becomes evident that other factors than the caseload prevail. The better outcome for oesophageal cancer surgery that Verhoef et al. described in our region might therefore not be attributed to the university hospital on basis of the highest volume but other hospital related qualities.[19] This might also be the case for the benefit described by Bachmann et al., based on the difficulty to distinguish this volume aspect from other hospital related qualities.[22] Quality of initial surgical care, for example extended lymphadenectomy, not fully reflected by operative mortality rates might play a role next to patient care in the follow up period after surgery. Enzinger et al. suggested delay in time of recurrence because of their observation that survival based on volume differences appear during the first 3 years after surgery.[28]

It is interesting that comparison of the two observation periods showed an improvement in survival during the later period limited to distal cancer. The most likely cause of such differences is stage migration due to better diagnostics. However this would not readily explain the lack of improvement in proximal cancers.

In conclusion the hospital type in our region did not significantly influence outcome of surgery for gastric cancer. For future consideration however, gastric cancer surgery will require the guaranteed availability of multidisciplinary oncological teams experienced in multimodality treatments.

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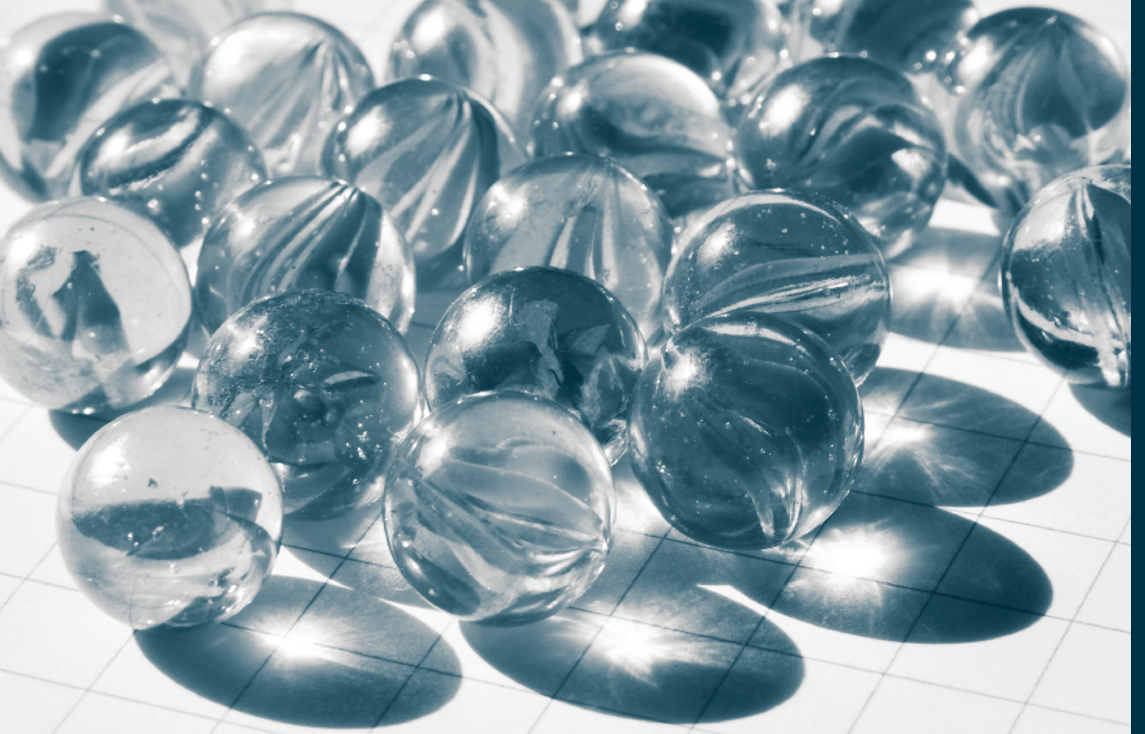

Chapter 6

Short- and long term outcome of gastric cancer in octo- and nonagenarians in North East Netherlands in the period of 1994 -2006, a population based study

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Abstract

Background: In the next decade not only the number of octo- and nonagenarians with gastric cancer will rise, but this group will also be more heterogeneous. Reluctance towards extensive surgery in this age group still is high, although single centre studies show a favourable outcome. This population based study aims to support decisions in this particular age group, by exploring patient and treatment related factors important for outcome.

Methods: From 1994-2006, 1251 patients, 80 years or older, were diagnosed with gastric adenocarcinoma in the Comprehensive Cancer Centre North-East Netherlands region. Information was collected with regard to patient, tumour and hospital characteristics. Survival on the short and long-term was determined by linkage with the national automated population registry.

Results: Only 351 out of 1251 octo- and nonagenarians with gastric cancer were operated. Fewer operations were performed in nonagenarians and in case of advanced or unknown stage ($p<0.001$). Postoperative mortality (61-days) was only associated with age and as high as 38.1% in patients 85 years or older. However when patients survived an operation long term outcome was acceptable with a median survival of 17.4 months (95 % Confidence Interval (CI); 13.5 -21.4 months). The 5-year relative survival was 41.5% (95% CI; 33.3-50.3%) and the 5-year overall survival 16.3% (95% CI; 11.2-22.2%).

Conclusion: Although long-term survival is acceptable, the postoperative mortality in octo-and nonagenarians after gastric cancer surgery is too high. Better selection procedures and improved perioperative care are needed to reduce surgery related mortality, next to studies open for this age group.

Introduction

The ageing of the general population poses an increasing challenge for the health care system. By 2015 a demographic shift will have emerged towards old age, with 20% more people aged 65 years and over, and 50% more aged 80 years and over[1]. Today the majority of patients treated in hospitals are already in their seventies. In the Netherlands 65% of the outpatient clinic population is older than 65 years (www.cbs.nl). But in the next decade especially the prevalence of octo- and nonagenarians will rise dramatically. In 2050 in the group over 65 years, 4 out of 10 people will be older than 80 years (www.cbs.nl).

Compared to the still somewhat rare very old patients who are treated today, this future group of patients is more heterogeneous, as improved care allows many more chronically ill patients to reach these advanced ages[1]. Today in the Netherlands 4% of the general population is 80 years or older, one in three having more than one chronic disease (www.cbs.nl). With advancing age also other factors, related to frailty and important for the life expectancy, change. This means that in the near future not only the fit elderly, but also more frail patients, with more co morbidities, will require treatment. Because of the different structure of the elderly population over the next years, the established treatment paradigms for the ailments particular to this age group need to be reviewed regularly.

As the incidence of solid tumours increases with age a considerable fraction of those octo- and nonagenarians will present with a diagnosis of a malignancy. In our region already 18% percent of all cancers are diagnosed in patients 80 years or older. In this older age group gastric cancer is prevalent. Due to the demographic developments the absolute number of newly diagnosed gastric cancers in the Netherlands is expected to rise with 44% between 2005 and 2025 (www.cbs.nl). Current treatment strategies for gastric cancer often incorporate chemo- and/or radiotherapy next to surgery. A few decades ago curative surgical treatment for especially the very old was considered highly unusual. Today, with advanced surgical techniques and improved postoperative care it is questionable whether this is still the correct approach. Several recent, mostly single centre, studies suggest that curative surgery can be performed at an acceptable risk and with reasonable good outcome in this age group[3-5]. More informative, compared to single centre studies, are data on outcome from population based studies. To support decisions about the best treatment options for octo-or nonagenarians we have analysed retrospectively a large cohort of patients with gastric cancer in the North-east region of the Netherlands. In these patients we have recorded the choice of treatment; surgery or not and compared outcome in two periods to identify possible changes in patient- and treatment factors.

Patients and Methods

Patients

Information on octo- and nonagenarians with primary invasive gastric cancer in the period 1994- 2006 was retrieved from the Comprehensive Cancer Centre North-East Netherlands registry. This population based registry covers the North-eastern part of the Netherlands, an area with 3.3 million inhabitants, that is served by one university hospital and 22 community hospitals, among which 8 teaching hospitals.

The regional cancer registry collects information on all newly diagnosed cancer cases submitted by regional pathology laboratories. Trained registry clerks complete case ascertainment directly from patient records, including pathology and surgery reports. Data collection occurs at a minimum of 6 months after diagnosis in order to document all aspects of the primary treatment. All patients are staged according to the TNM system. Vital status is established through linkage of cancer registry data with the national automated population registry. Date of initial surgical resection was registered in the Northern region in the period of 2002-2006, data from the Eastern region were recorded from 2004 onwards. Surgery included all patients, those with a curative and palliative intent.

Variable definitions and Statistics

Postoperative mortality was defined as all deaths occurring within 61-days after initial surgery. Survival time was calculated from the date of diagnosis and ended at the date of death or the date of most recent linkage with the national automated populated registry, whichever came first. The 5-year overall survival was calculated using the Kaplan Meier method. The distribution of overall survival time was compared with the log rank test. The cumulative relative survival, the ratio of the overall and the expected survival, calculated using age, sex and period matched mortality rates from regional life expectancy tables (www.statline.cbs.nl/StatWeb), was also calculated. Multivariate analysis of relative survival uses the property that the ratio of two relative survival rates can be considered an excess mortality ratio. Excess mortality rates are calculated by subtracting the expected number from the observed number of deaths and dividing this figure by accumulated person-years. The excess mortality ratio is given by the ratio of two excess mortality rates. Multivariate excess mortality ratios were

estimated in a generalized linear model with a Poisson error structure based on collapsed relative survival data[6].

Results

Patient and hospital characteristics

In the period of 1994-2006 a total of 1251 patients, 80 years or older were diagnosed with gastric cancer of which 646 patients were male. The number of established diagnosis declined with age, with 148/1251 patients presenting at age 90 years or older. An operation was rarely performed in these nonagenarians compared to the octogenarians, respectively 13/148 versus 338/1103 (p<0.001).

A small part of the adenocarcinoma histology showed signet ring cells (107/1251). Differentiation grade in most cases was poor (435/1251) or unknown (525/1251).

Most tumours were located in the antrum and pylorus region (417/1251). These distal tumours were much more operated on compared to proximal tumours (46.8% versus 8.9%, p<0.001).

In many cases (509/1251) no stage classification was available and in this group an operation was rarely performed (2/509). Furthermore when patients were staged, often advanced disease was diagnosed, with 416/1251 tumours in stage III or higher. With advanced stage less operations were performed, respectively 61.7% in stage I, 78.1% in stage II, 59.8% in stage III and 18.7% in case of stage IV disease (p<0.001). In the very small minority of patients who received chemo- or radiotherapy (respectively 1/1251 and 49/1251) an operation was never performed (Table 1).

There were no differences in age and stage distribution or tumour location for operated patient between the teaching and non-teaching hospitals (Table 2).

Post-operative mortality

Table 3 shows postoperative mortality of the patients according to patient, tumour and hospital characteristics from 2002 onwards. In total 17 out of 91 patients died within 61 days after surgery. Only patient age was associated with postoperative mortality. Patients aged 85 years or over had a markedly increased probability of post-operative death, 8/23 versus 9/68 in patients of 80-84 years.

There was no difference in postoperative mortality between teaching and nonteaching hospitals, respectively 11/48 versus 6/43 of the operated patients died within 61 days after surgery.

Table 1.

Characteristics of patients diagnosed with gastric adenocarcinoma between 1994-2006, aged 80 years or over, all patients combined, operated and non-operated patients

		Total	Operated		Not operated	
		N	N	%	N	p-Value*
Gender	Men	646	185	28.6	461	0.637
	Women	605	166	27.4	439	
Age at diagnosis (years)	80-84	717	249	34.7	468	<0.001
	85-89	386	89	23.1	297	
	90-94	128	11	8.6	117	
	95+	20	2	10.0	18	
Histology	Adenocarcinoma, nos	1019	285	28.0	734	<0.001
	Mucinous	60	33	55.0	27	
	Signet ring cell	107	33	30.8	74	
	No microscopic confirmation	65	0	0.0	65	
Tumour location	Cardia&fundus	260	23	8.9	237	<0.001
	Body&curvature, nos	210	71	33.8	139	
	Antrum&pylorus	417	195	46.8	222	
	Overlapping & unspecified	364	62	17.0	302	
Differentiation	Good	39	20	51.3	19	<0.001
	Intermediate	252	106	42.1	146	
	Poor	435	179	41.2	256	
	Unknown	525	46	8.8	479	
Stage	Stage IA	70	42	60.0	28	<0.001
	Stage IB	142	90	63.4	52	
	Stage II	114	89	78.1	25	
	Stage III	122	73	59.8	49	
	Stage IV	294	55	18.7	239	
	Unknown	509	2	0.4	507	
Therapy	Surgery	351	351	100.0	0	<0.001
	Chemotherapy	1	0	0.0	1	
	Radiotherapy	49	0	0.0	49	
	Other/none	850	0	0.0	850	
Total		**1.251**	**351**	**100.0**	**900**	

* p-Values apply to Chi-square or Fischer's exact test where applicable

Table 2.

Stage and age distribution for operated patients aged 80 years or over, according to hospital type were surgery was performed 1994-2006, stratified by tumour subsite

		Total N	Teaching N	Non-teaching N	p-Value*
Stage	Stage IA	42	29	13	0.162**
	Stage IB	90	48	42	
	Stage II	89	52	37	
	Stage III	73	50	23	
	Stage IV	55	29	26	
	Unknown	2	1	1	
Age (yrs)	80-84	249	151	98	0.280**
	85-89	891	53	36	
	90+	13	5	8	
	Median (IQR***)	82.9 (81.4-85.5)	83.0 (81.4-85.4)	82.8 (81.4-85.8)	0.548
Tumour location	Cardia & fundus	23	16	7	0.597**
	Body & curvature, nos	71	43	28	
	Antrum & pylorus	195	113	82	
	Overlapping & unspecified	62	37	25	
Total		**351**	**209**	**142**	

*** p-Values apply to Chi-square tests, ** excluding stage unknown, *** IQR=Inter Quartile Range**

Figure 1a.

Relative survival for gastric cancer patients aged 80 years or over

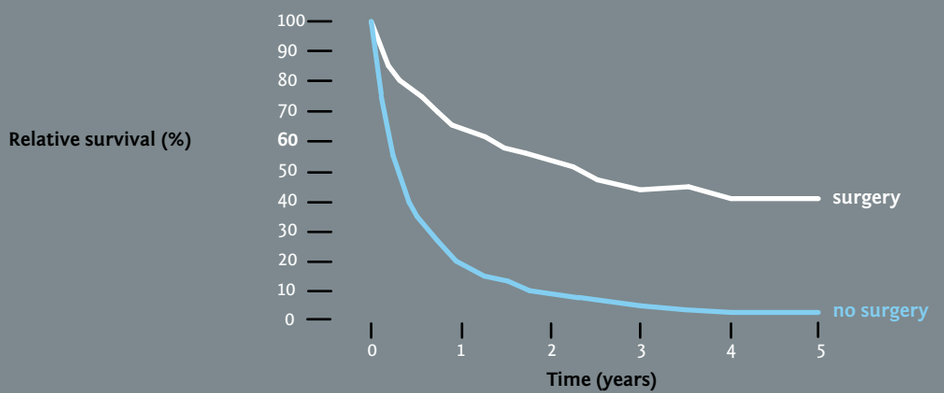


Table 3.

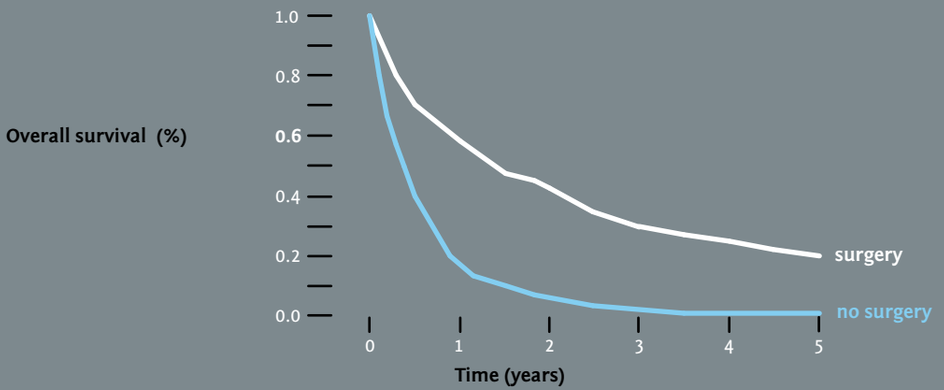
Post-operative (61-day) mortality for patients aged 80 years or over, operated in the period 2002-2006

		Patients N	Post-operative mortality N	%	p-Value*
All patients		91	17	18.7	
Age (years)					
	80-84	68	9	13.2	0.054
	85-89	21	8	38.1	
	90+	2	0	0.0	
Tumour location	Cardia & fundus	4	0	0.0	0.685
	Body & curvature, nos	24	3	12.5	
	Antrum & pylorus	40	9	22.5	
	Overlapping & unspecified	23	5	21.7	
Stage	Stage I**	36	4	11.1	0.454
	Stage II	17	4	23.5	
	Stage III	19	5	26.3	
	Stage IV	19	4	21.1	
Hospital type* **	Non-teaching**	43	6	14.0	0.297
	Teaching	48	11	22.9	

*** p-Values based on Fisher's exact test, ** Reference group, *** Teaching status based on surgical subspecialisation**

Figure 1b.

Overall survival for gastric cancer patients aged 80 years or over



Number at risk	**Surgery**	204	141	97	72	58
	No surgery	141	47	20	7	5

Table 4.

Overall and relative 5-year survival and estimated excess risk of death with 95% confidence intervals (95% CI) for operated gastric cancer patients aged 80 years or over, diagnosed 1994-2006

		All operated gastric cancer patients				
		Univariate		Multivariate		
		5-year OS	5-year RS	EMR	95% CI	p-Value*
Sex	Males	16.3	38.3	1.00		0.536
	Females	26.1	44.8	0.89	0.62-1.28	
Age (years)	80-84**	24.8	42.7	1.00		0.070
	85-89	11.7	31.8	1.57	1.05-2.35	
	90+	7.7	24.5	1.72	0.64-4.64	
Period	1994-2000	21.0	41.1	1.00		0.351
	2001-2006	20.0	40.1	0.83	0.56-1.23	
Tumour location	Cardia & fundus	19.6	35.6	1.00		0.339
	Body & curvature, nos	22.5	43.2	0.92	0.39-2.11	
	Antrum & pylorus	22.5	45.2	0.83	0.38-1.79	
	Overlapping & unspecified	13.6	26.1	1.25	0.55-2.82	
Stage	Stage I**	35.7	70.3	1.00		<0.001
	Stage II	20.2	38.8	2.35	1.30-4.24	
	Stage III	9.2	17.6	3.92	2.21-6.94	
	Stage IV	2.3	3.8	7.11	3.97-12.72	
Hospital type***	Non-teaching**	19.2	38.1	1.00		0.665
	Teaching	22.0	43.5	0.93	0.65-1.32	

OS=Overall Survival, RS=Relative Survival, EMR=Excess Mortality Risk, 95% CI=95% Confidence Interval;
* p-Values apply to multivariate model, adjusted for time since diagnosis, ** Reference group,
*** Teaching status based on surgical subspecialisation

Table 5.

The median overall and relative survival (in months) and estimated excess risk of death with 95% confidence intervals (95% CI) for not-operated gastric cancer patients aged 80 years or over, diagnosed 1994-2006

		All not-operated gastric cancer patients				
		Univariate		Multivariate		
		Median OS	Median RS	EMR	95% CI	p-Value*
Sex	Males	3.4	3.7	1.00		0.688
	Females	2.7	2.8	1.03	0.88-1.20	
Age (years)	80-84**	3.4	3.6	1.00		0.286
	85-89	2.8	3.1	1.07	0.90-1.20	
	90+	2.0	2.8	1.20	0.95-1.51	
Period	1994-2000	2.9	3.0	1.00		0.790
	2001-2006	3.3	3.5	0.98	0.84-1.14	
Tumour location	Cardia & fundus	4.1	4.4	1.00		0.006
	Body & curvature, nos	3.8	4.1	0.94	0.74-1.21	
	Antrum & pylorus	2.8	3.2	1.03	0.83-1.28	
	Overlapping & unspecified	2.2	2.3	1.31	1.07-1.59	
Stage	Stage I**	3.9	4.4	1.00		<0.001
	Stage II	5.8	7.1	0.99	0.58-1.68	
	Stage III	4.2	4.4	1.35	0.89-2.03	
	Stage IV	2.2	2.3	2.15	1.60-2.89	
	Stage unknown	2.9	3.7	1.27	0.96-1.67	

OS=Overall Survival, RS=Relative Survival, EMR=Excess Mortality Risk, 95% CI=95% Confidence Interval;
* p-Values apply to multivariate model, adjusted for time since diagnosis** Reference group

Survival

In the patients who underwent an operation median survival was 17.4 months (95% Confidence Interval (CI); 13.5 -21.4 months) and the 5-year relative survival was 41.5% (95% CI; 33.3-50.3%) with a 5-year overall survival of 16.3% (95% CI; 11.2-22.2%) (Figure Ia and Ib). The 5-year relative survival was 38.3% for men compared to 44.8% for women. Although survival decreased with age, after multivariate analyses relative survival in the operated group was not statistically significantly different when comparing octogenarians (80-84 yrs 42.7%, 85-89 yrs 31.8%) and nonagenarians (24.5%) (p=0.070).
Patients who presented with stage I disease and were operated on had a 5-year overall survival of 35.7% and a 5-year relative survival of 70.3%. However relative survival decreased rapidly with more advanced stage, and was respectively 38.8% in stage II, 17.6% in stage III and 3.8% in stage IV disease (p<0.001). Survival for operated gastric cancer patients did not improve during the study period, with respectively a 5 year relative survival of 41.1 in the period of 1994-2000 and of 40.1 in the period of 2001- 2006 (Table 4). Neither the location of the tumour, proximal or distal, nor the type of hospitals where the operation was performed influenced outcome in this particular age group.
In those patients in whom no operation was performed median survival was 3.0 months (95% CI 2.6-3.6 months) with a 5-year relative survival close to zero (Table 5).

Discussion

Until the beginning of the last decade of the previous century, reluctance towards gastric cancer surgery in patients older than 70 years was high, as advanced age was considered to be one of the highest risk factors for postoperative morbidity and mortality[7]. In the late nineties it was recognized that it was save to perform these operations in septuagenarians, as far as morbidity and mortality were concerned, through studies from Bittner and Msika[8,9]. However in the near future due to demographic shifts, not only septuagenarians but also increased numbers of octo- and nonagenarians are going to develop gastric cancer. Reluctance towards operation for this particular group is still high.
Recent population based studies indeed showed a high risk of postoperative death after gastric cancer surgery in the very old. A postoperative mortality rate as high as 24% in octogenarians and 44% in nonagenarians was observed in these studies[10-12]. Our results are in line with these data, especially in the group 85 years and older, as

one in three patients died within two months after surgery. However some recent retrospective single centre studies provide evidence that operation is indeed feasibel also in octogenarians. These studies showed a postoperative mortality between 3.8-11.6%[4,5,13]. Japanese series even reported zero postoperative deaths[14,15]. Identifying the clues to this contradiction might help to recognise patient and surgical selection procedures that would improve results in the general population.
The single centre studies do provide some evidence that excluding octo- and nonagenarians with co morbidity could improve postoperative morbidity results[4,13,16]. Another factor emerging from these single centre studies as being important in the deselection of the very old is advanced disease[17]. Higher mortality rates are reported in case of locally advanced disease leading to non-curative surgery or the presence of distant metastasis[13]. Marrelli et al even observed a fatality rate of complications 5 times higher in case of non-curative surgery (50%) compared to curative procedures (10%)[4].
The extend of the surgery can also be an important factor in explaining the differences in short-term outcome between single centre and population based studies. The surgical approach most often chosen in the single centre studies in octo- and nonagenarians is subtotal gastrectomy (65-80%) instead of total gastrectomy[4,5,13,15]. In the elderly population total gastrectomy has been reported to be associated with a higher postoperative mortality risk around 10%[18]. This association was confirmed in a recent survey on gastric cancer in 1611 patients in 18 population based cancer registries within Europe. In this survey in the general population postoperative mortality after total gastrectomy (12.4%) was nearly twice as high as that after subtotal gastrectomy (6.6%)[19].
Finally, some single centre studies reported a more than three times higher number of operations performed in the very old per year compared to the centres in our study[4,5,13]. In the Japanese studies not only a large number of octo- and nonagenarians was operated on, but the total number of gastric cancers operation per year (range 71-440) was impressive[5,14,15,20]. Therefore these centres are very high volume hospitals. High surgical volume has in many but not in all studies[21] been reported to be associated with better post-operative survival. Especially the Japanese studies therefore might serve as arguments for centralization of gastric cancer surgery at least in this advanced age group. A confounding factor remains that most studies that report favourable post-operative survival do not report on the percentage of deselection for surgery.

Selection for surgery takes into account the biological age that refers to the human functional capacity. The functional decline in an elderly patient is a highly individualized multidimensional process. The value of calendar age in octo- and nonagenarians as a selection criterion for adverse events after surgery and as predictor of life expectancy is therefore limited. In the process of ageing, in addition to co morbidity, other domains such as cognitive, social and psychological capabilities are especially important. This loss of resources in several domains of functioning is captured in the term frailty. According to Schuurmans et al using frailty as the criterion to select older patients instead of calendar age leads to better selection of patients at risk for interventions[22]. Such criteria can be found in selection instruments such as the multidimensional Comprehensive Geriatric Assessment (CGA)[23]. Other practical or investigational instruments in this area have been described[24]. Hopefully it might therefore be possible by using those assessments to improve postoperative survival rates, whether by deselection for surgery or optimizing the patient's condition preoperative, like nutrition status.[25] Improving surgical and post-operative care could further optimize outcome on the short-term. Minimally invasive surgical procedures, such as laparoscopic gastrectomy, have been advocated to improve peri operative morbidity and mortality[26]. However definitive results of randomised trials, in which frailty is also recorded, have to be awaited to substantiate that both short term and long term oncological results offer hope for the future treatment of this advanced age group.

The long-term survival of the operated octo- and nonagenarians in our population-based study was acceptable and comparable to outcome in the general population. Due to a possible selection bias, i.e selection of more fit elderly with stage I and II disease for an operation, relative survival might overestimate disease specific survival for this group of patients, because the expected survival for this patient group is based on the survival in the complete population of, say, patients aged 85-89. This would give too optimistic expectation for the survival gain, in terms of gastric cancer specific survival, for the operated patients. Although even overall survival will be biased due to selection of the less frail patients for surgery, it is clear that life expectancy is much better for patients who underwent surgery, especially those with stage I or II disease, when we compare survival for operated with that of non-operated patients.

The 5-year survival rate of 41.5% which we observed overlapped with that reported by others[4,13], again Japanese series reporting the best 5 year survival[14,20]. In our study the long term outcome did not improve in the later years compared to the earlier period. This was also observed by a French population-based study that found a short lived improvement in long term survival, among patients aged 80 years or over, in the last decade of the previous century, that halted in later years[27]. Recently, advances in long-term survival have been described by the use of neoadjuvant chemotherapy[28]. However these studies did not include or report the percentage of patients older than 80 years[27] and its careful application should therefore be awaited.

Selection could mitigate the impact of surgery on patients; however it will not lessen the number of deselected patients. For these patients and for those who relapse, measures to improve all aspects, quality and duration, of life are needed. Evidence suggests that palliative chemotherapy in advanced gastric cancer can prolong survival compared to best supportive care (BSC)[29] and improve QoL[30]. In these trials, age 75 years or older, was an exclusion criterion. In the general population, compared to BSC, the months gained with single agent chemotherapy is about 6 months, or 10% of the natural life span in our particular age group, more toxic combination chemotherapy might even increase the survival further[29]. As for pre-operative chemotherapy, advantages of palliative chemotherapy in the very old are yet not clear. A recent review of the International Society of Geriatric Oncology chemotherapy Taskforce (SIOG) however showed that excessive toxicity of chemotherapy agents often used in gastric cancer such as fluoropyrimidines, platinum compounds and taxanes could not be attributed to age, but was related to organ dysfunction such as renal capacity or co morbidity[31]. In the new era, effects of biologicals such as trastuzumab, might outbalance that of cardiac complications.

In conclusion, this study confirms that successfully operated octo– and nonagenarians with gastric cancer have a satisfactory survival. The post-operative mortality was however high and independent of hospital type. Better selection procedures, assessing frailty, and improved peri-operative care are needed to reduce surgery related mortality. For improvement in long term outcome and better palliative care, appropriate studies open to patients from this age group, employing chemotherapy and biological response modifiers are eagerly awaited.

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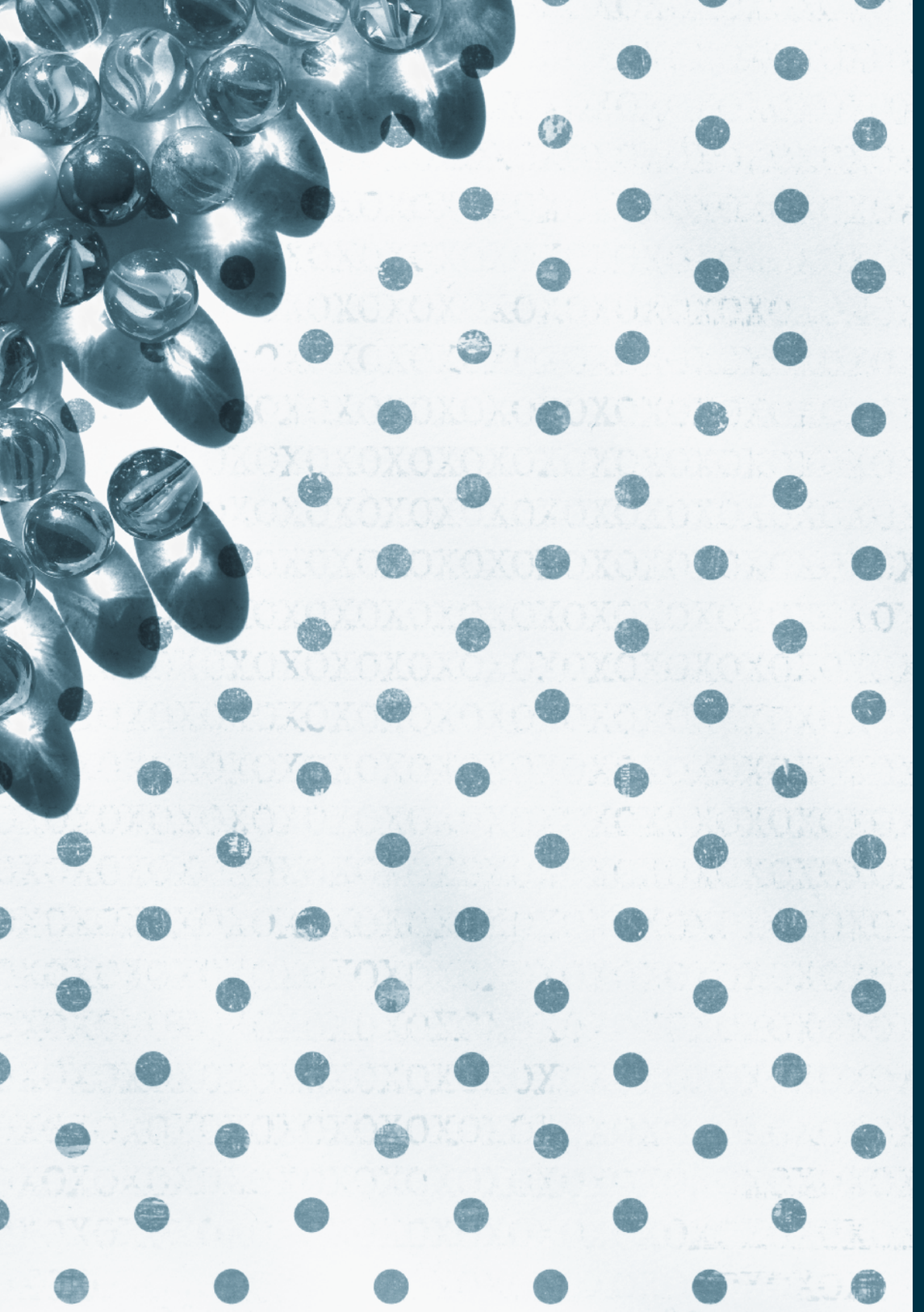

Chapter 7

Probable cure of two patients with advanced gastric carcinoma by chemotherapy only: Long-term follow-up of a phase I trial with a weekly carboplatin and epirubicin regimen

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Abstract

A dose escalation study of carboplatin in combination with 5FU and epirubicin in surgically incurable gastric cancer. Carboplatin was combined with a fixed dose epirubicin 35 mg/m^2, leucovorin 250 mg/m^2 and 5-FU 500 mg/m^2 (CELF). The starting dose of carboplatin was 100 mg/m^2, which was escalated to 150 mg/m^2. This CELF regimen was repeated every week, for a maximum of 14 cycles. Primary prophylaxis against leukopenia with filgrastim was given. Twelve chemotherapy naive patients were enrolled, 9 with metastatic disease and 3 with locally advanced surgically incurable disease. The major toxicities of the CELF regimen were uncomplicated leukopenia and thrombopenia. Nausea and mucositis were the most common non-haematological toxicities. The dose-limiting toxicity was grade 3 leukopenia, observed at a dose of 150 mg/m^2/week. The objective response rate was 58% (95% CI 31%-85%). From the three patients, with localized but surgically incurable disease, two remained alive without disease progression and without symptoms after 6 and 9 years after chemotherapy without any other treatment.

Introduction

At the end of the last decade of the twentieth century a multitude of chemotherapy regimens were investigated for the treatment of surgically incurable gastric cancer[1]. Differences between regimens were especially at the level of toxicity rather than the antitumor activity was concerned. Cascinu reported in 1997 on an active intensive weekly regimen with a high response rate[2]. Essentially the compounds used in this regimen were by that time emerging to become the standard of care for incurable gastric cancer. In the previous years 5-fluorouracil (5-FU) had been the mainstay of treatment as it had demonstrated that its use improved overall survival and quality of life compared to best supportive care (BSC) in several randomized trials[3,4,5]. Subsequently, from all drugs added to 5FU especially cisplatin and epirubicin or adriamycin seemed to improve on the results of 5-FU alone. The 3 weekly regimens were most commonly used in these comparisons till today, but it was not yet standard when the current weekly regimen was tested. Based on those data we performed a study of Cascinu regimen with a modification of the platinum compound in order to improve the feasibility and tolerability of this intensive weekly regimen. Triggered by the long-term clinical results we report on the mature data.

Material and Methods

In august 1998, we initiated this phase I dose finding study in chemotherapy naive patients with metastatic and/or surgically incurable locally advanced gastric carcinoma in the university hospital in Groningen, the Netherlands.

Eligibility criteria

All patients had to have histological proven, measurable gastric carcinoma, either surgically incurable locally advanced disease or metastatic disease. Age was 18 – 60 years, with an ambulatory performance status of 0-1 on the Eastern Cooperative Oncology Group (ECOG) scale and a life expectancy of › 3 months. Laboratory acceptance parameters included a white blood cell count ≥ 4.0 x 10^9/L, platelet count ≥ 150 x 10^9/L, serum bilirubin ≤ 1,5 x upper limit of normal, and calculated creatinine clearance of ≥ 80 ml/min.
Additional eligibility criteria included the absence of clinical signs of myocardial ischemia, no serious active infections requiring antibiotics, no clinical signs of brain metastasis, no concurrent radiotherapy and no previous chemotherapy. Pregnant or lactating women were not eligible as were patients with previous or current malignancy

at other sites with the exception of squamous cell carcinoma of the skin or in situ carcinoma of the cervix uteri. All patients gave written informed consent before entering this study. The study protocol was approved by the institutional review board.

Study design

Before study entrance, patients underwent a complete history and physical examination, including performance status and weight. Base line imaging studies were obtained to define the extent of the disease. Laboratory tests included a complete blood cell count with differential and platelet count, blood chemistry studies and urine analysis.

In order to define the maximum tolerated dose (MTD) of carboplatin in combination with epirubicin, 5FU and leucovorin, escalating doses of carboplatin were added to fixed doses of epirubicin, 5-FU and leucovorin. The starting dose of carboplatin was 100 mg/m^2/week in the first four patients. In the absence of toxicity exceeding WHO grade 2 on leucocytes and platelets in the first three weeks of treatment, the next cohort of four patients were planned to receive carboplatin 150 mg/m^2/week. In case of no haematological toxicity exceeding WHO grade 2 in this cohort, the next dose level was 200 mg/m^2/week. In case of toxicity WHO grade 3 or 4 on leucocytes and or platelets during the first three weeks of treatment, this was considered dose-limiting toxicity. In case of 2 patients with dose-limiting toxicity on a given dose level the level below this level was considered to be the maximum tolerated dose. The carboplatin dose was de-escalated to the prior dose level for the following courses. Planned doses of chemotherapy were given if white blood cells count ≥ 4.0 x 10^9/L and platelets ≥ 100 x 10^9/L, otherwise treatment was delayed for one week until full recovery. In the case of grade 2 or 3 mucositis or diarrhoea treatment was also delayed for one week until recovery.

The outpatient chemotherapeutic regimen consisted of a 1-day per week (day 1) administration of Carboplatin as a 30-min i.v. infusion; epirubicin 35 mg/m^2 as an i.v. bolus infusion; leucovorin 250 mg/m^2 as a 60 min split i.v. infusion before and after 5-FU; 5 FU 500 mg/m^2 as a 15 min i.v. infusion. From day 2 till day 6 patients received G-CSF 5 μg/kg subcutaneous. As anti-emetic therapy patients received ondansetron before and after chemotherapy administration. After 8 weeks of treatment tumour re-evaluation was performed and patients with a tumour response or stable disease, according to WHO criteria were planned to have a further 6 weeks of treatment. Treatment was stopped in case of progression or any grade 4

non-haematological toxicity. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 2.0.

Statistical analysis

The analysis of this phase 1 study is primarily descriptive. Values are presented as median with ranges unless stated otherwise. Pearson's correlation was used to calculate the relation between carboplatin dose and toxicity.

Results

Patient characteristics

During the study period a total of 12 patients, 8 men and 4 females, with a median age of 55 years (range 32-62) were enrolled. Nine patients had stage IV disease and three had locally advanced surgically incurable disease. (Table 1)

Treatment characteristics

The first four patients were treated at the 100 mg/m^2 carboplatin level, without dose-limiting toxicity during the first three cycles. Subsequently the next four patients were treated at the 150 mg/m^2 carboplatin dose level. In this dose level, one patient had grade 3 leukopenia in the third cycle and one grade 4 with septicaemia in the fifth cycle. As defined by protocol the following patients were treated at a dose of 100 mg/m^2 carboplatin. 121 Treatment cycles were applied in this study. The median number of cycles administered was 10 per patient (range 4-14). Dose reductions and delayed administration of cycles resulted in a dose intensity of respectively 81% in the 100 mg/m^2 carboplatin dose level, at the 150 mg/m^2 carboplatin dose level the dose intensity was 67%, and 85% of this reduced intensity was due to delayed administration. Since we expected that frequent dosing, dose density, is one of the features to increase the therapeutic index, the frequent delays and even a delay of 3 weeks in the 150 mg/m^2 carboplatin dose level, combined with a complicated grade IV leukopenia in the fifth cycle, led to the conclusion that 100 mg/m^2 carboplatin was the MTD.

Toxicity

All patients were assessable for toxicity (Table 2). Haematological toxicity, diarrhoea and nausea were the major toxic effects of CELF chemotherapy. One patient with evidence of response based on reduction of a supraclavicular lymph node, had a gastric perforation,

possibly due to the tumour response. This was considered grade IV toxicity so treatment was stopped, and the patient died 5 months later. The median dose of carboplatin based on AUC using the Calvert formula, was 1.63 mg/ml*min (range 1.41 to 1.94) in the 100 mg/m^2 group, and respectively 2.60 mg/ml*min (range 2.29-3.0) in the 150 mg/m^2 group. We did not find a relation with relative platelet count reductions in the first 3 cycles and carboplatin target AUC (R=0,24)

Tumour response

All patients had measurable lesions. Eight patients completed 8 weeks of treatment until the first planned response evaluation; so four patients were lost for response evaluation and considered non-responders. Of these four patients one patient had probably progressive disease, based on clinical findings. Two patients refused further treatment after respectively 4 and 6 cycles; one of them was evaluated and had stable disease. In one patient the treatment was stopped after 5 cycles due to gastric perforation, however clinical findings indicated response. Of the 8 evaluated patients after 8 weeks of treatment, 6 patients had a partial response (PR). In none of these patients additional surgical intervention was feasible. Two patients had a stable disease (SD), resulting in an objective response rate of 50% (95% CI 22%-78%) after 8 cycles.

One patient with PR refused further treatment after the first response evaluation; she had a complete response on a repeated tumour evaluation after 2 years. The remaining 7 patients had a second evaluation after the planned total of 14 cycles. One patient had a PR after a SD in the first evaluation. Two patients with a PR in the first evaluation had evidence of ongoing PR at the time of the second evaluation. For the other 4 patients the situation between the first and second evaluation was unchanged. Thus the overall objective response rate was 58% (95% CI 31%-85%) after 14 weeks. The median survival was 11.25 months (range 1.5 –100+months).

Of the 3 patients with locally advanced surgically irresectable disease one died of tumour progression after 24 months. However the other two patients are currently still alive with no clinical evidence of disease at respectively 9 and 6 years post treatment. The first patient had a stage IIIb, intestinal type adenocarcinoma and was treated at the 150 mg/m^2 dose-level (7 cycles) with an actual dose intensity of 77%, the second patient had a stage IIIb, undifferentiated adenocarcinoma and was treated at the 100 mg/m^2 dose-level with an actual dose intensity of 71% (13 cycles). Both long-term survivors received no additional treatment.

Table 1.

Patient and tumour characteristics

		Total	%
Number entered		12	
Median age in years		55 (Range 32-62)	
Sex			
	Male	8	(67)
	Female	4	(33)
WHO performance status			
	0	3	(25)
	1	9	(75)
Gastric cancer stage (AJCC)			
	IIIb	3	(25)
	IV	9	(75)
Histology			
	Diffuse	3	(25)
	Intestinal	9	(75)
Differentiation grade			
	Well differentiated	3	(25)
	Moderately differentiated	4	(33)
	Poorly differentiated	5	(42)

Table 2.

Toxicity of chemotherapy

	Carboplatin dose level 100 mg/m^2 (n=8, cycles 81) WHO grade				Carboplatin dose level 150 mg/m^2 (n=4, cycles 40) WHO grade			
	I	II	III	IV	I	II	III	IV
Mucositis	5	1	1					
Nausea	4	2			3	1		
Diarrhoea			1			2		
Leukopenia	9	4	3		9	4	1	1
Thrombopenia	25	6	2		10	5	1	1

Discussion

Although the incidence of gastric cancer declines it is still the world's second leading cause of cancer related death. The mainstay of treatment remains a radical surgical resection, which seems feasible in about 40 % of the patients (American Joint Committee on Cancer staging (AJCC) stage I-III). This results in a 5 year survival of approximately 58-95% in stage I, 34-54% stage II, 20-37% stage IIIa and 8-11% stage IIIb disease[6,7]. Even after apparent curative resections, local recurrences or distant metastasis occur in up to 60% of the patients. Unfortunately, most patients present with an advanced stage of disease with a dismal outcome. This group consists of patients with locally advanced surgically incurable disease (±30%) and patients with metastatic disease (±30%). In that situation the prognosis is worse with a median survival in case of locally advanced disease of 12-15 months and 7-10 months in case of relapsed or metastatic disease[8,9]. The last decade a lot of effort has been put into the development of more effective systemic therapies for those patients with advanced gastric cancer to improve quality of life and prolongate survival. At first multiple single agent regimens were tested, later much effort has been put in combination chemotherapy in order to improve response rate and survival. In these regimens 5-FU was combined with either etoposide and leucovorin (ELF), doxorubicin and methotrexate (FAMTX) or epirubicin and methotrexate (FEMTX). These treatments resulted in response rates of approximately 50% objective responses and 10% complete responses with median survival rates of 8 to 11 months, but essentially no long term survivors were reported[2,3,5,10,11]. Two randomized controlled trials were conducted using these 5-FU based regimens versus cisplatin and 5-FU based schedules. One study compared ELF or FAMTX versus cisplatin and 5-FU, with no significant differences in either response or survival[12]. The other study showed higher response rates for epirubicin, cisplatin and 5-FU versus FAMTX, with comparable survival rates[11]. The favourable response rate of the combination of epirubicin, cisplatin and 5-FU (PELF) was confirmed in a phase II trial in a weekly schedule[2]. Although high response rates do not necessarily translate into prolonged survival, they might be valuable in the neo-adjuvant setting and in the situation where a rapid palliation, for instance of obstruction problems, is required. A few years later the value of perioperative chemotherapy on survival in resectable gastric cancer was confirmed in the MAGIC trial[13].

At the moment that the weekly regimen caught our attention, the 3 weekly regimen was not yet considered standard treatment. The current study showed that the weekly CELF regimen was feasible in an outpatient setting with an acceptable toxicity at a carboplatin dose of 100 mg/m^2. Toxicity in the first three cycles of chemotherapy, limiting the dose dense intention of the schedule, was observed at a dose level of 150 mg/m^2. The MTD of 100 mg/m^2, induced in three cycles WHO grade III leukopenia and in two cycles grade III thrombopenia, during later cycles. Grade 3-4 toxicity data reported for the PELF regimen are comparable to the data reported here. The CELF regimen showed a promising response rate of 58% (95% CI 31%-85%) comparable to the objective response rate of 62% in the phase 2 study of weekly PELF.

The mature data on this weekly regimen show interesting and not expected long-term event free survival of two patients in this study of respectively 9 and 6 years. Both patients had locally advanced surgically incurable disease, one patient received 7 courses (150 mg/m^2 carboplatin) and one patient received 13 courses (100 mg/m^2 carboplatin) of CELF. Both had a partial response after chemotherapy, and at that time it was judged that curative resection was still not feasible. The fate of patients deemed surgically incurable is usually considered to be grim. In the era of best supportive care all patients die within 1 year after diagnosis[3,4,5]. Subsequently in the western world this group has been entered in chemotherapy studies, sometime recognizable in stratified subgroups; one or more metastasis or locally advanced disease[2,14-18]. In such patients an interesting 55.6 -68% 4-5 years survival have been reported in patients who were considered to be resectable after chemotherapy[2,14,19]. Especially in Japanese studies local treatments (extended surgery, local chemotherapy) have been added tot these regimens[20]. In this study only 3 long-term survivors, after only chemotherapy, out of 643 patients were described. One of them survived more than 5 years; two others ultimately succumbed to their disease[20].

In view of our results it seems not unlikely that a subgroup of patients with especially surgically incurable, but still limited disease, not only will have palliative benefit, but may even find cure from chemotherapeutic intervention.

Conclusion

Long-term follow-up of this feasible phase I trial, with promising response rates, uncovered two long-term survivors. Late evaluations of studies in gastric cancer patients are uncommon however for some subgroups of patients such analyses might be worthwhile. Based on our results we therefore would like to encourage other researchers to perform late analysis of data in order to help to discover patient and tumour characteristics resulting in long-term survivorship.

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Chapter 7a

Retrospective denial as a coping method

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Abstract

Worldwide, gastric cancer is one of the most common and fatal cancers. The majority of patients present with an advanced stage of disease. Even with use of palliative chemotherapy most patients die within one year after diagnosis. Medical psychological attention after a diagnosis of incurable cancer is focused on end of life support.

The case is presented of a patient treated with palliative intent with chemotherapy for an irresectable histologically confirmed gastric cancer. When, unexpectedly prolonged symptom free survival followed, the reaction of the patient came as a surprise to the attending medical team. In this case history we urge those who care for incurable cancer patients, that the rare patient who survives against all odds may require special psychological care.

In conclusion, unexpected developments, in this case prolonged survival, culminating in likely cure, require intensive efforts in adaptation of care.

Background

Gastric cancer is one of the most common and fatal cancers, affecting more males than females. Large differences exist in the incidence of gastric cancers between various geographic regions. In North America, Africa, Oceania 4-10 /100.000 people per year are affected, in northeast Asia up to 69 cases per 100.000 people per year[1].

It is now known that this cancer is generally the aftermath of Helicobacter Pylori (H. Pylori) infection. The risk for adenocarcinoma is 6-fold increased in those infected with H. Pylori. H. Pylori are a bacterium which can lead to chronic gastritis. However only a minority of patients infected with this organism develop cancer, concerting risk factors are high salt intake, low intake of vegetables or fruit, obesity and smoking[2].

Although the incidence of gastric cancer is declining due to preventive strategies, such as treatment of H. Pylori and better food preservation methods, it remains the second leading cause of cancer related death worldwide. Symptomatic patients often have complaints like weight loss, abdominal pain or dysphagia. Diagnosis is established by endoscopy, which is insertion of a flexible tube through the mouth[1]. Once the diagnosis is established by obtaining tissue scored by the pathologist as being malignant, therapy can be aimed at cure or be limited to some prolongation of life and mitigation of symptoms.

The only way to cure gastric cancer is by surgery. Because of the high recurrence rate after surgery alone most patients are also treated with some form of adjuvant (postoperative) or neoadjuvant (preoperative) chemotherapy, in the United States combined with radiotherapy. If surgery can be done requires CT scanning and often ultrasound[1]. Sometimes it is only during surgery that it becomes clear that the cancer has progressed beyond the surgeon's domain. In such advanced stages of gastric cancer, when the tumour has become irresectable, attention has to be focused on palliative measures. The emphasis in this phase is based on prolonging survival with preservation or improving quality of life. Care is then largely determined by the expectancy of approaching death. Although still a demanding clinical task, much literature and guidance is available for the clinician on giving optimal support. Compared to best supportive care several studies have described a beneficial effect of chemotherapy on quality of life, next to achievement of survival benefit. Compared to mono chemotherapy agents, combination chemotherapy gives additional survival benefit of some weeks to months, at the expense of more toxicity[3]. With the development of targeted agents against molecular signalling pathways a larger survival benefit might be accomplished.

Targeted therapy is a type of medication which blocks the growth of cancer cells by interfering with specific targeted molecules needed for tumour growth rather than interfering with rapidly dividing cells in case of traditional chemotherapy[1].
Next to chemotherapy or local palliative measurements physicians get trained in guiding patients on their way to approaching death, by listening to their complaints, desires and fears. Surprisingly little is known about the psychological consequences for the rare patient with unexpected long-term survival or cure against all odds, as described here.

Case Report

A middle-aged patient was referred after explorative laparotomy only because of irresectabel adenocarcinoma of the stomach.
Chemotherapy was instituted, but stopped because of excessive toxicity. The message communicated at that moment was gloomy based on the initial diagnosis and the residual lesions on CT-scan after chemotherapy. Even more than before the start of chemotherapy, the patient expected to die from this cancer and seemed to adapt to this situation, the more since a second opinion, confirmed the initial diagnosis and did not provide alternatives. However the patient remained in an excellent condition throughout the following years. Although one could assume that a patient would be relieved by being an exceptional long-term survivor, 9 years by now, the opposite occurred. Survival became a considerable psychological problem. Finally some form of equilibrium was found in a state of denial of ever having had cancer.

Discussion

The median survival of patients with advanced gastric cancer is 7 to 10 months. Chemotherapy can lead to palliation and prolongs survival with a few months. However long-term survival or cure after only a partial tumour remission on chemotherapy without surgery has rarely been described[3].
Apart from these medical considerations the most remarkable reaction of our patient was the psychological one. At first the patient accepted the diagnosis of irresectable gastric cancer and agreed to palliative chemotherapy. However, after remaining alive longer than expected without evidence of disease our patient reacted with a rare type of denial namely retrospective denial of the diagnosis.
Denial in cancer patients is a well recognized phenomenon in clinical practice[4-7]. Denial is the process by which the mind defends itself

against painful or threatening information. Depending on the situation this can be maladaptive, e.g. leading to treatment delay, or adaptive, e.g. enabling the patient to cope with this life-threatening disease. A recent review on denial in cancer patients distinguished four types of denial: denial of diagnosis, denial of impact, denial of affect, and behavioural escape[2]. Denial of diagnosis mostly takes place early in the process of diagnosis, and decreases over time, although it sometimes increases during the terminal phase[7].
Our patient, however, seems to be cured and denying having had cancer at first sight seems incomprehensible. Insight in this denial can be obtained from available knowledge on how people try to explain unpredictable life events. In general, people make different causal attributions for positive and negative events. Positive events mostly are considered to be the result of internal causes: people tend to ascribe success in life to themselves. Negative events are mostly attributed to external causes: failure due to circumstances. So, we could expect that our patient would refer being a survivor of cancer to these internal causes, such as a fighting spirit, or a healthy life style. Most patients will make causal attributions to external sources for the fact that they get cancer, clearly a negative event, in such a way that self-esteem is preserved[6].
When our patient stayed alive longer than expected, external rather than internal attributions were sought. Given the fact that the doctors were wrong about dying soon they could be wrong in other aspects of the disease too. If the patient did not believe in divine intervention, how could this unexpected outcome be explained?
The thought of not having cancer in the first place is in accordance with this unexpected outcome. Moreover, this conviction serves well to reduce anxiety and uncertainty about recurrence of cancer: a predominant preoccupation in most survivors of cancer[4,5]. There was no reason to be afraid that the cancer could come back if it had never been there! Although denial in this case is not a logical solution, it certainly is a psychological one. Thus for the patient the past experiences with life-threatening disease and the unexpected positive outcome are explained, and the fear of a recurrence of cancer is superfluous.
As a medical team we were unable to help the patient on the path from the certainty of death to unexpected survival. Whether the adaptation through denial of the patient to the new situation is the most desirable one is doubtful. Realization by us that good news may be as difficult to cope with as bad news might have provided a guideline for earlier psychological intervention.

Dialogue between Drs. Siemerink (junior Medical Oncologist), Dr. Jaspers (Psychologist) and Professor Mulder (senior Medical Oncologist) regarding the case:

Drs. Siemerink: Professor Mulder, how often did you observe unexpected prolonged survival among patients with advanced disease? And was there in your opinion a common reaction in your patients to that situation?
Professor Mulder: There are various levels of unexpected survival, most often reported in the context of some form of alternative medicine. In a review in our country some 400 reports of that kind were analyzed and only 2 could be accepted as undoubtful. If we give a prognosis of 8-12 months for a patient as described here we would expect an occasional patient to live for 2 years, some patients with breast cancer may survive for decades with metastatic disease. However for a patient treated in a palliative context to be cured, as in this situation, I can remember three in a period of some thirty years, all of them were extremely grateful, if not to me at least to their good fortune.
Professor Mulder: Dr. Jaspers, the reaction of our patient to survival, retrospective denial of the diagnosis of cancer, came as a complete surprise for the medical team. Is this reaction common in cancer patients?
Dr. Jaspers: Denial in cancer patients is a well recognized phenomenon in clinical practice, especially denial of diagnosis. However, it mostly takes place early in the process of diagnosis, and decreases over time. Sometimes it increases during the terminal phase. So, denial is a common reaction to bad news. What makes denial exceptionally in this case, is that it is a reaction to the good news of survival. Other causal attributions for this positive event could be expected. People normally attribute positive events to internal causes, in the case of cancer survival for instance to their fighting spirit or to their change of lifestyle. When a patient attributes his survival to his own behaviour or characteristics, there is no need to deny the fact that he had cancer.
Drs. Siemerink: At first we did not understand the reaction of the patient who was very angry at us and was convinced that we had failed as doctors and caused much sorrow.
Dr. Jaspers: Indeed, at first sight it seems incomprehensible that a positive progress of the disease made the patient react this way. But from the point of view of the patient, if it would be true that cancer had never been there the emotions can be understood. The patient

was told that this disease was fatal and treated invasively for a disease which was not there.
Drs. Siemerink: So, the retrospective denial of the diagnosis is a way of coping with this unexpected positive course of the disease?
Dr. Jaspers: Cancer is a disease that brings much uncertainty and loss of control for patients. In general there is little they can do, except rely on medical treatment and hope for the best. Loss of control is hard to deal with, and research on coping with cancer shows that at least half of the surviving patients experience positive effects (post-traumatic growth) of having cancer. Some consider these positive effects as a way of coping to regulate feelings of anxiety and depression (illusionary growth), others consider these positive experiences as real growth.[8] Retrospective denial of the diagnosis is an effective way to regain control and at the same time eliminate anxiety and uncertainty about recurrence of cancer.
Professor Mulder: At the other hand, denial as a way of coping seems unrealistic. Can denial be an effective coping method?
Dr. Jaspers: Denial is the process by which the mind defends itself against painful or threatening information. Mostly denial does not last long, because it is only temporarily necessary to regulate and control negative emotions. In the long run denial is often inadequate, because it hampers adaptation to the altered situation, for instance having cancer. So, it depends on the circumstances whether denial can be an adequate or inadequate coping strategy. In the case of this patient denial not only explains the unexpected cure of cancer, but also seems to have positive effects on the long run (reduce anxiety about recurrence of cancer). So, may be in this case denial is not a bad strategy for the patient as long as this strategy has no evident disadvantages for the patient. There may be another reason for this unexpected attribution. In general, people have a strong urge to seek causal attributions for their behaviour or for the events they experience. The cure of irresectable gastric cancer cannot be explained. It is hard for people to live with such events of vital importance that cannot be explained. So, retrospective denial of the diagnosis makes sense, because it explains the inexplicable: it is better to have an improbable explanation than no explanation at all.
Drs. Siemerink: What can we learn from this case? The reaction of the patient resulted in premature loss of contact with the patient. We realized too late that the good news was difficult to cope with.
Dr. Jaspers: Indeed, the first lesson to learn from this case is that good news may be as difficult to cope with as bad news. To realize this and to speak with the patient about this unexpected progress

and the possible confusing impact of it can be the first step. To share feelings with the patient over this positive, but unlikely development can give the physician the opportunity to consider whether psychological intervention is indicated. Doubts about the diagnosis can be discussed earlier by the patient when he feels he is free to do so without direct rejection of this possibility. I think, physicians should respect this opinion of the patient, bearing in mind that this attribution has a psychological function. Direct attempts to refute this opinion only increases resistance to chance or reconsider this opinion and hinders to discuss other issues for example how to adapt to the fact that life is not over yet and the patient can plan for the future again. Perhaps, for some physicians the conviction of the patient that the diagnosis was wrong is a difficult one, because their expertise is called in question. Of course, the patient has the right to be informed about all aspects of his disease, but sometimes the truth of the medical team is not the truth of the patient.

Dr. Jaspers: how are you as a young oncologist trained in dealing with these difficult situations of providing information about the fatal course of a disease in general but also staying focused on the individual patient?

Drs. Siemerink: In our traineeship much attention is paid to communication of bad news and the different ways a patient can react to this news at diagnosis, for example by patient simulation and watching video's. However this specific situation of sustained denial was not something I was prepared for.

Professor Mulder: If we had recognized the problem earlier, and had consulted a psychologist, would he have tried to reverse this process? In other words, given that the patient has reached some form of equilibrium, can we consider this to be a satisfactory situation? Not quite unconnected is the question if it is likely that at some time the patient will realize that cancer indeed had occurred.

Dr. Jaspers: I don't think the reason for consulting a psychologist should be to convince the patient of the correctness of the diagnosis of cancer, but to explore with the patient what contrary to all expectations, this unexpected survival means for the patient. I think it is important for the patient to express (mixed) emotions and to talk about the reactions to this confusing course of the disease. Undoubtedly, in talking about the situation the question will arise: 'How can this be?' It is hard to speculate whether this patient would have considered other answers than the conviction that cancer never had occurred, but I suppose that earlier in the process this idea is still more open for discussion. When the patient is still looking for an

answer, the psychologist can explain that it is our human nature to attribute causes to all important events that we experience, also the events that perhaps are inexplicable. So, it may be difficult to realize that certainty about the cause of progress of the patient's disease cannot be found. But, if the patient is already convinced that the doctor was wrong in his diagnosis, I think it would be wise to respect this opinion, given the psychological function that we discussed before. This does not mean the psychologist has to agree with the patient: he can state that – just like the medical team – he cannot give an explanation for this unexpected development. What the psychologist can do for the patient is to sort out how to adapt to this new situation, prevent obsessive preoccupation and rumination, and how to get on with life, leaving this stressful period of illness behind. When the patient succeeds in this respect, the urgency to blame the physicians for the alleged faults they made will be less, and the conclusion that the patient was very lucky in the end can be acceptable.

Drs. Siemerink: Finally a question that, perhaps, cannot be answered: should this extraordinary case change the information we give an incurable patient or if there is no statistical hope should we still provide it?

Dr. Jaspers: In the last decades there has been a major change in the way we talk about cancer and in our view how to inform the patient. Although the patient has the (legal) right to be informed fully, sometimes the truth and nothing but the truth can be too much to handle for the patient. Appraisal of the state of mind of the patient can be difficult and to bring the bad news of approaching death remains a demanding clinical task, but in general the information available should be given. Timing, choosing the right words and opportunity are important in telling the unwelcome truth, but this truth gives the patient and his beloved ones the opportunity to deal with it. So, when there is no (statistical) hope, no false hope should be given. When the patient needs hope to endure his situation, he will find it anyway, holding the truth is not a good way to provide hope.

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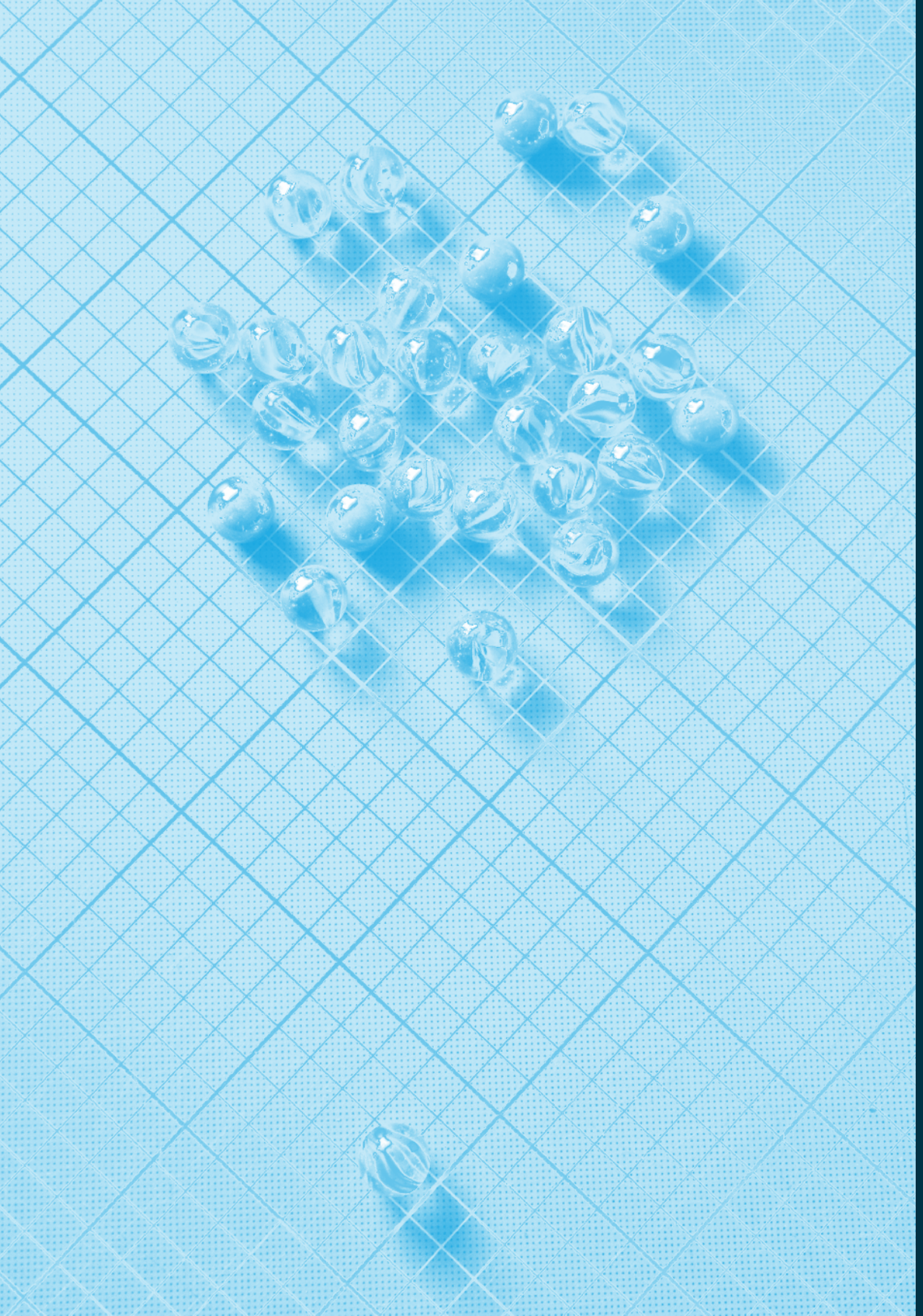

Chapter 8

Phase II study of Oxaliplatin, UFT, and Leucovorin in patients with metastatic gastric cancer

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Abstract

Background The present study evaluated the efficacy and safety of oxaliplatin, UFT, and leucovorin in metastatic gastric cancer.

Methods Patients received intravenous oxaliplatin 130 mg/m^2 on day 1, followed by oral UFT capsules (350 mg/m^2 per day) and leucovorin tablets (90 mg/day), every 8 h, for 14 days, in a 3-week cycle.

Results Twenty-three patients (61% with ≥ 2 metastatic sites), median age of 60 years (range, 36-69 years) were entered. Based on intention-to-treat analysis, one complete response and seven partial responses were found, resulting in an overall response rate (RR) of 35% (95% confidence interval (CI), 16-54), a median time to progression of 4 months (95% CI, 0.5-7.5) and a median overall survival (OS) of 8 months (95% CI, 4.5-11.5). The 1-year survival rate was 26%. Three patients did not complete the first course of 2 weeks; 1 died suddenly on day 16 with fatal lung embolism, 1 had rapid progressive disease and 1 experienced gastric haemorrhage on day 15 - both these patients withdrew. In the 20 patients assessable for toxicity no grade 4 toxicity occurred, grade 3 toxicity consisted of anaemia in 1, diarrhoea in 2 and neurotoxicity in 3 patients. No hand-foot syndrome (HFS) occurred.

Conclusions Oxaliplatin is an effective drug in gastric cancer, but, as previously reported, its feasibility in combination with capecitabine is hampered due to combined hand-foot-based toxicity. The present phase II study of a combination of oxaliplatin with UFT and leucovorin appears to have efficacy and tolerability comparable to other two drug regimens used in gastric cancer, without the HFS problem.

Introduction

Gastric cancer is the world's second leading cause of cancer related death. Unfortunately, most patients present with an advanced stage of disease, with a dismal outcome. Even after apparently curative resections, local recurrences or distant metastasis occur in up to 60% of the patients[1,2].

In this palliative situation patients do benefit from combination chemotherapy compared to best supportive care, as it shows modest survival benefit, with improvement of quality of life[3-6]. 5-Fluorouracil (5-FU) is still one of the main chemotherapeutic agents used in advanced gastric cancer with a response rate (RR) as mono-agent of 21% and a median survival of 6-7 months, while at the same time epirubicin, cisplatin and 5-FU (ECF) is the most widely used combination regimen. With an overall RR of ECF of 40-45% and a median survival around 8-10 months it is considered a reference regimen especially in Europe[2,7-10]. In the context of quality of life, the observed toxicity, prolonged hospital time due cisplatin infusion and risks of central venous access devices and ambulatory infusion pumps, the use of the combination regimes instead of mono chemotherapy is debatable. There is a need for an effective chemotherapy combination which is less toxic and can be easily administrated in an outpatient setting. In order to improve convenience and tolerability three oral fluoropyrimidines have been developed[11,12]. One of them is UFT, a combination of Tegafur, an oral prodrug of 5-FU which is slowly metabolized in the liver into the active drug 5-FU and Uracil, a competitive antagonist for dihydropyrimidine dehydrogenase (DPD), in a 1:4 M ratio. Uracil inhibits degradation of 5-FU because it competes with 5-FU for DPD, leading to higher intra-tumoural 5-FU levels. This combination drug has a RR of about 16-57 % and an median overall survival (OS) of 5.8 to 15 months and is less toxic as far as myelosuppression, stomatitis, diarrhoea, and Hand-foot syndrome (HFS) are concerned[11-16]. Clinical studies in metastatic colon cancer have shown that UFT has a comparable efficacy profile compared to intravenous bolus administration of 5-FU[17,18]. Capecitabine, the oral fluoropyrimidine most often used worldwide, has a toxicity and efficacy profile similar to UFT, except that HFS, which is rarely observed in UFT, occurs in more than half of all patients treated with capecitabine[19,20]. The third oral fluoropyrimidine S-1 has not been registered in Europe, and is licensed in Korea and Japan[11].

Oxaliplatin is a third generation platinum derivative, which inhibits replication and transcription by formation of DNA adducts. It has shown anti-tumour activity as a mono-therapy or in combination with 5-FU and leucovorin (LV) in various solid tumours, including

gastric cancer. In comparison with cisplatin it has a more favourable toxicity profile, with substantially lower rates of myelosuppression, nefrotoxicity and ototoxicity, but with at least equivalent activity[21-24]. The duration of intravenous hydration required with cisplatin use is not required for oxaliplatin, hereby facilitating outpatient administration. In combination with other chemotherapeutic agents, the UFT/LV schedules that are often used are UFT doses of 300-400 mg/m^2/d, and LV doses of 25-500 mg, for 1-14 treatment days per 21 days or 1-28 treatment days per 35 days[11]. In combination with a fluoropyrimidine, oxaliplatin is given in a 2- or 3-weekly schedule with an intravenous (i.v.) dose of respectively, 85 and 130 mg/m^2 [25-27].

Based on these promising data of two different active agents with little overlap in terms of key side effects, we conducted a phase II study with oxaliplatin (130 mg/m^2 on day 1), UFT capsules (350 mg/m^2 day), LV tablets (90 mg/day), every 8 h, for 14 days, in a 3-week cycle in patients with metastatic gastric cancer, in an outpatient setting, to investigate the anti-tumour activity and toxicity of this combination regimen.

Patients and Methods

Eligibility

Between February 2004 and September 2008, patients with histologically confirmed metastatic gastric cancer with at least one measurable lesion according to the response evaluation criteria in solid tumours (RECIST) criteria were considered to be eligible in this open, non-comparative phase II study.

All patients were age › 18 years with an ambulatory performance status of 0-1 on the Eastern Cooperative Oncology Group (ECOG) scale and a life expectancy of more than 3 months. Laboratory acceptance parameters included adequate haematological (white blood cell count 4.0 x 10^9/L), hepatic (serum bilirubin ‹ 1,5 x upper limit of normal), and renal (calculated creatinine clearance of › 50 ml/ min) function. Exclusion criteria consisted of: bone metastasis or effusions as only manifestation of disease; clinical signs of brain metastasis; concurrent radiation therapy or previous chemotherapy; previous or current malignancies at other sites; evidence of serious active infections; severe cardiac and/or pulmonary failure, and pregnant or lactating women.

The study was approved by the ethics review board of our hospital (METC 2004.016) and carried out in accordance with the Declaration of Helsinki principles. Written informed consent was obtained from all patients with a 7-day interval after thorough information had been given about the study.

Pre-treatment evaluation

Pre study assessment consisted of full medical history, vital signs and physical examination. Further investigations included haematological and blood chemistry testing, electrocardiogram, chest X-ray and a computed tomography (CT) scan of the abdomen.

Treatment schedule

Oxaliplatin (130 mg/m^2) was administrated by a 2 h i.v. infusion on day 1 followed by oral UFT capsules (350 mg/m^2 per day) and LV tablets (90 mg/day) taken simultaneously every 8 h from the evening of day 1 to the morning of day 15, followed by a 7-day treatment free interval in a 3-week cycle. After two and four cycles, patients with a tumour response or stable disease continued on chemotherapy, receiving a maximum of 6 cycles.

Dose modifications

In patients with non haematological toxicity of grade 2 or greater, treatment was postponed until toxicity resolved to grade 1 or less; the next UFT dose was reduced by 25% in patients with grade 3-4 toxicity. With haematological toxicity of grade 2 or greater, treatment was withheld until the white blood cell count was 3.0 x 10^9/L or greater and the platelet count was 100 x 10^9/L or greater. The oxaliplatin dose was reduced by 25% in case of persistent (14 days) paresthesia or temporary painful paresthesia or functional impairment. Treatment was discontinued in case of grade 4 non haematological toxicity or non-recovery of persistent paresthesia, and in those with non haematological toxicity of grade 1 or greater despite a 2-week delay.

Treatment response and toxicity

Tumour response was evaluated on a CT-scan after cycles 2 and 4, and after the treatment was finished. The tumour responses were classified according to the RECIST. All patients were examined on days 1 and 15 of each cycle for vital signs, including physical examination, ECOG performance status and complete blood counts and biochemical tests. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 2.0.

Statistical analyses

For the determination of the number of patients required in a preliminary and follow-up trial of a new chemotherapeutic agent, the Gehan's two-stage design was used[28]. We expected a response rate

Figure 1.
progression free survival (months)

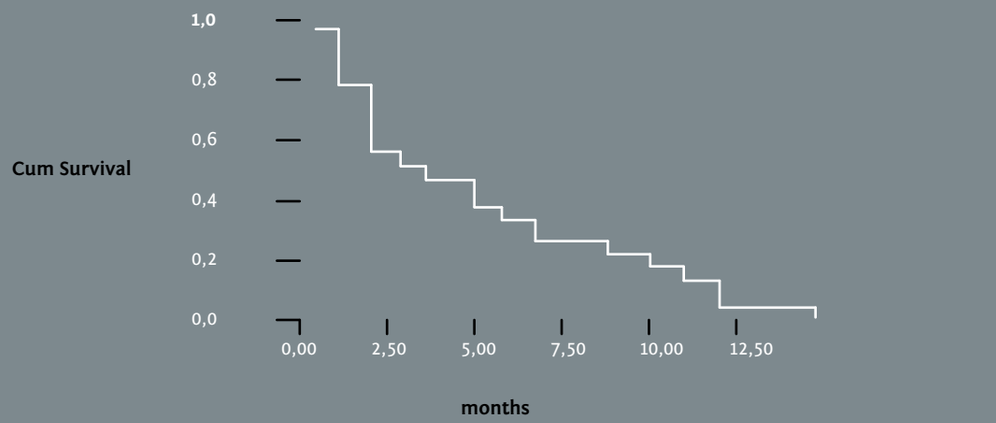
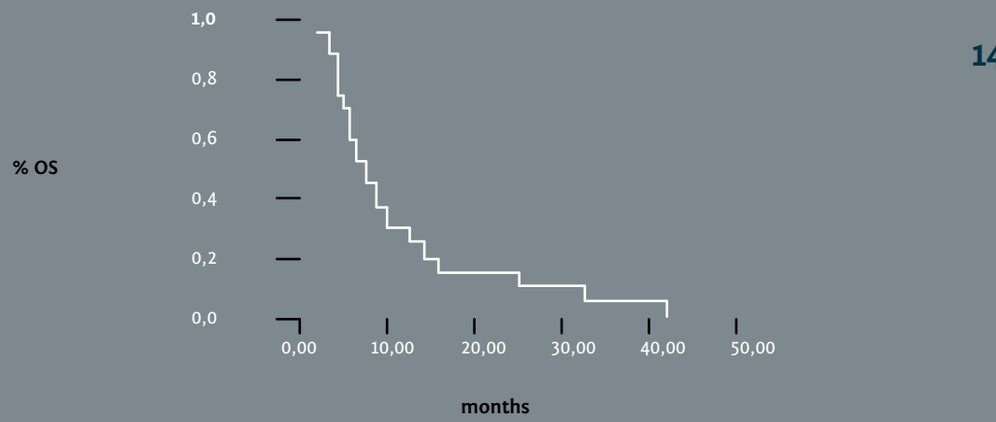


Figure 2.
Overall Survival (months)



of 30% or greater. If no objective response was seen in the first 12 patients, then the probability of a response rate of 30% or greater would be below 5% and no additional patients would be entered. If, in the first 12 patients more than four responses occurred, 8 additional patients were required for the evaluability of response. With a dropout frequency of 10%, 23 patients had to be included to estimate the 95% confidence interval (CI) for a true response rate with a maximum width of 38%.

Results

Patient Characteristics

During the study period a total of 23 patients, 21 men and two women, with a median age of 60 years (range, 39-69) were enrolled. Eighty percent of these patients had a performance score up to 1 at the start of treatment. Most patients (21/23) had a metastatic disease at time of diagnosis, while 2 patients developed metastatic disease after surgical resection of the primary tumour. The most common metastatic sites were liver, lung, bone, or peritoneum (83% of the patients), while 17% of the patients had only lymph nodes metastasis. Two or more metastatic sites occurred in 61% of the patients. At the evaluation in November 2009 all 23 patients had died.

Efficacy and survival

Twenty of 23 patients were assessable for toxicity, while the remaining 3 did not complete the first course of 3 weeks. One patient died suddenly on day 16 with a clinical diagnosis of fatal lung embolism, and a second patient had rapid progression of pulmonary metastasis and withdrew. The third patient who still had his primary tumour in situ, experienced a gastric haemorrhage on day 15 and withdrew.
All efficacy data are reported using the intention-to treat patient population.
The overall RR was 35% (95% CI,16-54); one patient had a complete remission, seven patients had a partial response, eight patients had stable disease and four patients had progressive disease. The median time to progression was 4 months (95% CI, 0.5-7.5) and the median OS was 8 months (95% CI, 4.5-11.5); see Figs. 1 and 2. The 1-year survival rate was 26%. Three initially responding patients in this study received second-line chemotherapy. One patient progressed after 1.5 year and was treated with irinotecan because of disease progression; however, this treatment was without an objective response. The two other patients progressed, after 6 and 8 months, respectively, and were treated with the oral fluoropyrimidine capecitabine; however, this treatment was also without an objective response.

Toxicity

The patients received a total number of 86 cycles (median, 3.5 cycles; range, 1-6). Nine patients received the maximum of 6 cycles. The most common reported toxicity was oxaliplatin-related sensory neuropathy, in 11 patients. Usually this was mild and reversible, with a need for dose reduction of oxaliplatin in only 3 patients. Other non haematological toxicity consisted of diarrhoea in 6 patients (2 with grade 3 toxicity), grade 1/2 nausea in 7 patients, and grade 1 weight loss in 5 patients. Haematological toxicity observed were grade 2 anaemia in 1 patient and grade 2 thrombocytopenia in 8 patients, and grade 3 anaemia in 1 patient. No grade 4 haematological or non-haematological toxicity was reported (Table 1). Eventually, treatment-related reasons for discontinuation were: persistent thrombopenia after 2 weeks of postponing the next cycle in 3 patients (after cycle 3,4,5, respectively), grade 3 diarrhoea in 2 patients, with need for hospitalization and clinical worsening in 1 patient and recurrent diarrhoea after dose reduction in the previous cycle in the other patient. The gastric haemorrhage that occurred on day 15 might have been treatment-related. The fatal lung embolism that occurred in cycle one did not seem to be treatment-related.
Treatment was also discontinued due to clinical tumour progression in four patients, and due to tumour progression on CT-scan in three patients. After discontinuation because of prolonged thrombocytopenia, two patients continued off study on mono UFT/LV.

Discussion

There is currently no universal standard regimen for the treatment of advanced gastric cancer. Two drug regimens often consist of a cisplatin and fluorouracil combination. In a palliative situation this regimen is not very patient-friendly, as hospitalization is often required, as is the use of continuously intravenous infusion.
Compared with the overall RR in the literature, with ECF and epirubicin, oxaliplatin, capecitabine (EOX) regimens showing RR of 38-47% and a median survival around 8-11 months, the results of our study showing an overall RR of 35% and median OS of 8.0 months, are similar but on the lower boundary[2,7-10]. This may be due to a relatively large number of patients showing early progression in our study who could not complete the first course. Our study also included patients with a relative high stage of advanced disease, as 61% of the patients had two or more metastatic sites, compared with 36-40% of the patients in the randomized ECF for advanced and locally advanced esophagogastric cancer 2 (REAL-2) study[7]. Based on the remaining

Table 1.
Toxicity

NCI-CTC grade	1	2	3	4
Hand foot syndrome	-	-	-	-
Neuropathy	2	6	3	-
Diarrhoea	1	3	2	-
Nausea	4	3	-	-
Weight loss	5	-	-	-
Thrombocytopenia	-	8	-	-
Leukopenia	1	-	-	-
Anaemia	1	1	1	-
ASAT	2	1	-	-
ALAT	2	3	-	-
Bilirubin	-	-	-	-

NCI-CTC, National Cancer Institute Common Toxicity Criteria; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase

evaluable 20 patients in the present study, our combination chemotherapy of oxaliplatin, UFT, and LV showed an acceptable antitumor activity with an RR of 40% and a median OS of 9 months, and could be safely administrated on an outpatient basis.

Several phase II-III studies have already indicated that oxaliplatin-based doublets may represent an effective and well-tolerated treatment option, compared to cisplatin, for patients with advanced gastric cancer[7,29-32]. In a study by Cunningham, oxaliplatin, compared to cisplatin, showed significantly less grade 3/4 neutropenia, alopecia, and thromboembolism, with significantly more grade 3/4 diarrhoea and peripheral neuropathy. This prompted these authors to the conclusion that oxaliplatin could replace cisplatin[7]. The results of a study by Al-Batran et al. are consistent with the REAL-2 data that oxaliplatin is at least as effective as cisplatin in patients with advanced gastric cancer[33]. The results of these two studies are comparable regarding neurotoxicity with the generally mild and reversible neurotoxicity observed in our study; in which all patients with grade 3 neurotoxicity could continue on treatment after dose reduction. As patients prefer oral to iv therapy provided that no more side effects occur and efficacy is not compromised, UFT and LV are a logical alternative for intravenous 5-FU[15]. Different phase II studies have investigated the efficacy of UFT with LV in combination with another agent[11,34-36]. These efficacy results are comparable with the RR of 35% and confidence interval of 16-54% in our study.

More often studies in patients with advanced gastric cancer use the oral fluoropyrimidine capecitabine. The REAL-2 data and the study of Okines et al. showed at least similar efficacy of intravenous fluorouracil and the oral fluoropyrimidine capecitabine[7,37]. The all-grade HFS was high in all groups (ECF 29.8%; epirubicin, cisplatin, capecitabine (ECX) 45.9%; epirubicin, oxaliplatin, 5-FU (EOF) 28.9%; EOX 39.3%). Moreover in the patients receiving capecitabine with epirubicin and cisplatin, significantly more grade 3/4 HFS was observed (grade 3/4; 10.3%) than in the ECF group (grade 3/4; 4.3%)[7]. Another recently published phase II study also emphasized the problem of HFS, which occurred in 39% of the patient population receiving capecitabine and oxaliplatin[32]. The problem of hand-foot-based toxicity, interfering with quality of life in a palliative situation is disturbing. In our study, as in many other studies with UFT-based combinations, patients hardly reported any HFS (< 0.01%). This observation forms the basis for replacing the oral fluoropyrimidine capecitabine by UFT. The efficacies of two-drug combinations with UFT are comparable with those of other capecitabine-based regimens, with reported overall RRs of 35-49% and

median os rates of 6 -11 months[2,11,30,38].

For the future new promising targeted biologic agents, often combined with chemotherapeutic drugs, are investigated. Although biologic agents are seemingly less toxic, epidermal growth factor receptor (EGFR) inhibitors can cause severe paronychia, and more commonly, acneiform rash[39]. Based on the toxicity profiles of UFT and capecitabine, it seems to be more logical to combine UFT with these new targeted biologicals.

In conclusion, based on the REAL-2 data, oxaliplatin has an important place in the first-line treatment of advanced gastric cancer[7]. However, the use of oxaliplatin in combination with capecitabine has led to an increasing number of patients with hand-foot problems. Therefore, combining an UFT/LV-based regimen with oxaliplatin in patients with advanced gastric cancer has the advantage of a good tolerability profile, with no HFS, and the regimen can be easily administered in an outpatient setting. For future studies with the new targeted agents, a combination of such agents with UFT would seem to be superior in dealing with the problem of hand-foot toxicity.

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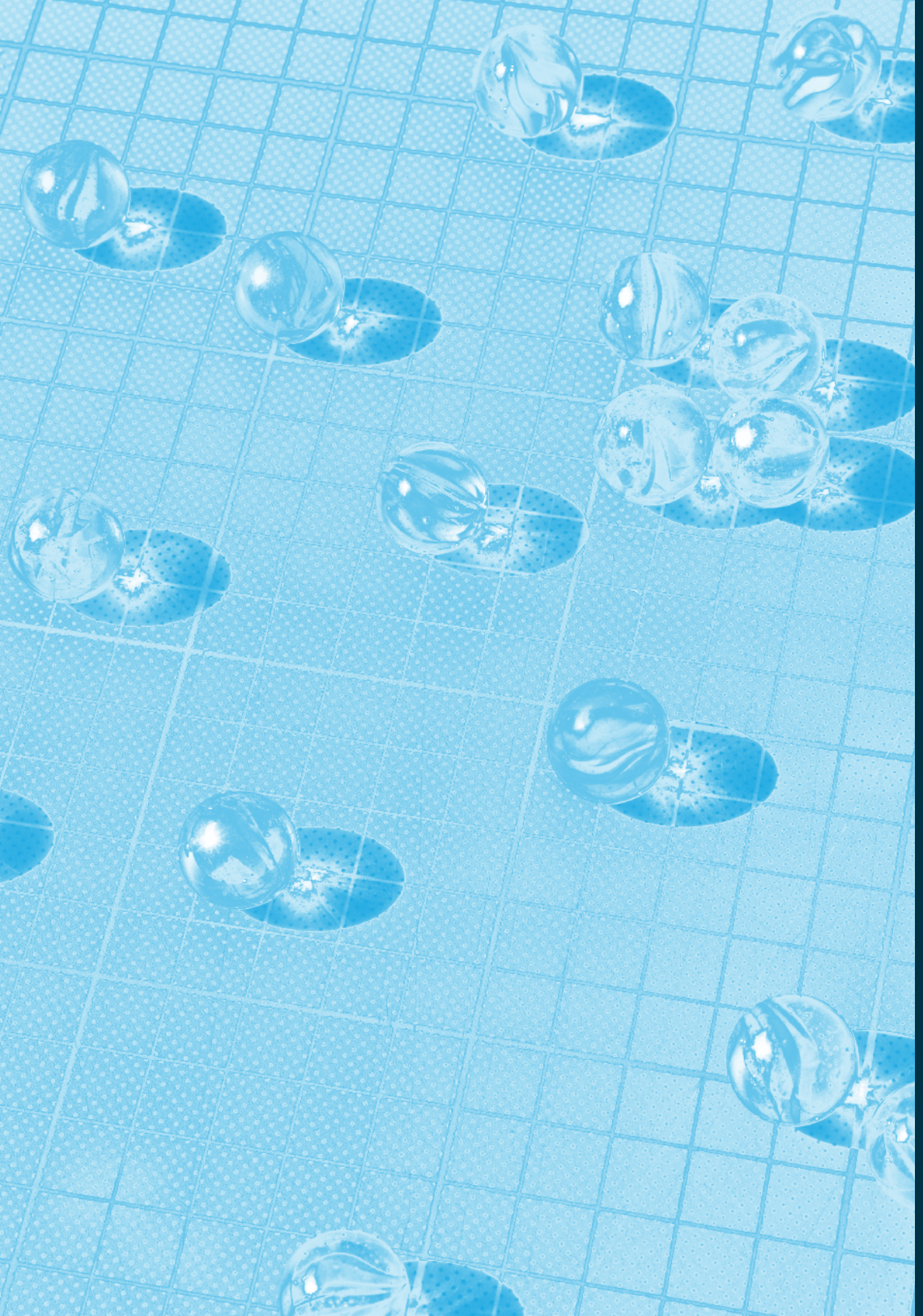


Chapter 9

Summary

Summary

Worldwide, gastric cancer is still the fifth most frequent cancer, and the second most frequent cause of cancer related death. The persisting high fatality rate of this disease is an interplay of multiple factors, patient, tumour and treatment related.

This thesis focussed on three issues regarding outcome of gastric cancer. Firstly, differences in patient characteristics which could lead to disparities in diagnosis, treatment and ultimately survival. Secondly, differences in hospital variables influencing outcome. Thirdly, two chapters were dedicated to the majority of patients, those with an advanced stage of disease, who can not be cured, and their treatment options and restrictions.

In CHAPTER 1 we presented an overview of the current perspectives on gastric cancer, regarding aetiology, diagnostic modalities and treatment options in curative and palliative setting. The risk of developing gastric cancer is considered an interaction between a bacterial risk factor as in Helicobacter Pylori next to host and environmental risk factors.

A genetic predisposition for gastric cancer has been described in families with atrophic gastritis, hereditary nonpolyposis colorectal cancer or in families who fulfill the criteria of hereditary diffuse gastric cancer (HDGC). The lifetime risk of deve-loping gastric cancer within HDGC families, in patients with a *CDH1* mutation is high and is estimated >80%. In CHAPTER 2 we reported the geno-/phenotypical data of all, in total 10, Dutch families with *CDH1* mutations. We observed a variable penetrance of gastric cancer between and within the Dutch families. Most carriers underwent prophylactic gastrectomy, revealing in most cases multiple foci of intramucosal carcinoma, with diffuse spread signet ring cells, that were not detected at screening. In *CDH1* families females are also at risk of developing lobular breast cancer (LBC). The incidence of LBC was remarkable low in the Dutch families. As it is expected that due to prophylactic gastrectomy mortality of gastric cancer can be prevented, the incidence of LBC probably will rise. Also because of the difficulty to detect LBC with screening, we recommended discussing prophylactic mastectomy as an option with female *CDH1* mutation carriers. Finally we observed a high incidence of cleft lip/palate, which supports the hypothesis that *CDH1* mutations are involved in the disturbed lip and palate closure. To establish the true impact of this observation further research is warranted in a larger patient cohort, in order to inform future parents from HDGC-families at genetic counselling.

High salt intake, smoking and Helicobacter Pylori infection are the more widely recognized environmental risk factors for gastric cancer, but also obesity and gastro oesophageal reflux are prevalent. The risk of developing gastric cancer is also increased in patient with low socioeconomic status (SES). In CHAPTER 3 we described the influence of SES on survival of gastric cancer in the North East region of the Netherlands. SES proved to be an independent prognostic factor for survival, with a lower risk of dying of gastric cancer in the higher SES group. For the patients living in high SES neighbourhoods the resection rate was higher as was the administration rate of chemotherapy. Moreover in the low SES group patient's diagnosis was established at older age. Nevertheless the statistical analysis showed neither type of treatment nor age, gender, histological grade, tumour localisation and stage alone were, as single factors responsible for the survival advantage. Obviously the interrelation of patient, tumour and treatment factors surprisingly was strong enough to level off the advantage of distal cancer prevailing in the low SES group, and the disadvantage of high grade tumours in the high SES group.

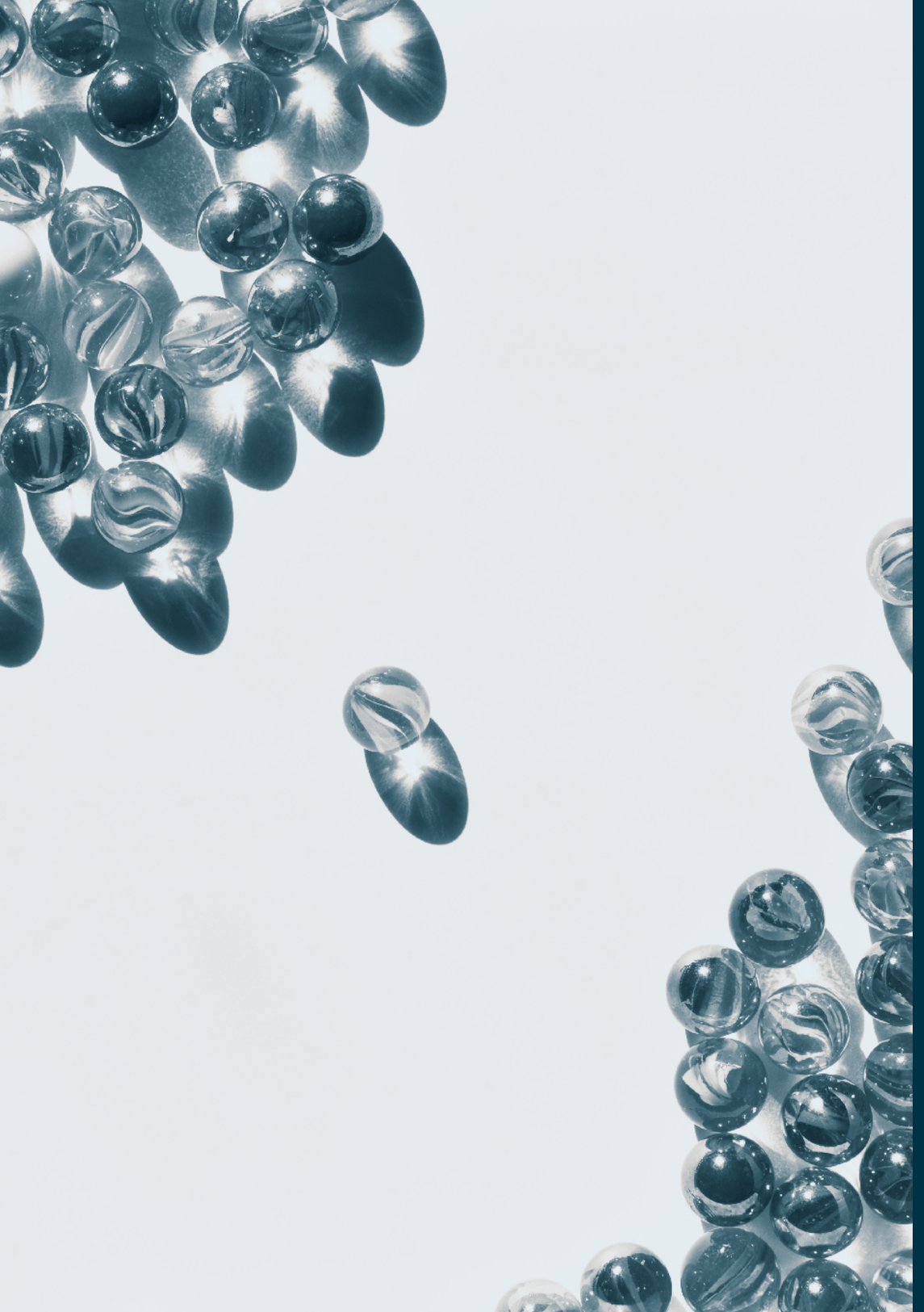
The purpose of the Dutch health care system, financially based on an obligatory insurance coverage, is to provide high quality health care and make it available to all citizens. Still disparities in health care access and outcome can develop in groups that are isolated in some way; social, cultural, religious and or communicative. To monitor the equality or difference in the care system a disease like gastric cancer can serve as a surrogate marker, as outcome is highly dependent on early detection. In this thesis, in CHAPTER 4, we analyzed survival of a group at risk of receiving suboptimal care; first generations non-western immigrants in the North East region of the Netherlands. Surprisingly outcome of gastric cancer in this group was better compared to western immigrants and autochthonic patients, also after adjusting for confounding factors. This difference could not directly be explained, but we could conclude that accessibility of the health care system does not seem to be hampered for this group of immigrants. We hypothesized that possible favourable factors were the social cohesion within this group of immigrants and the typical Dutch professional network ("the arbodienst").

Factors that are neither patient nor tumour related can also contribute to the outcome of curatively intended surgery in cancer patients. For example the influences of hospital volume and type as well as the surgical experience on the ultimate survival remain indeterminate. In CHAPTER 5 we reported data on outcome of gastric cancer in our region with regard to hospital characteristics. Between the 15 non teaching hospitals, 8 teaching hospitals and the only academic

centre we did not observed a role of teaching status or referral pattern on long term outcome. Within the small window of number of operations performed per year in our region no striking differences were found of hospital volume in relation to survival. In univariate analysis the 5-year relative survival of distal cancers seemed better in the academic hospital but this was not confirmed in multivariate analysis. This might be explained therefore by selection bias, because on average younger patients were operated on in the academic centre. This issue of patient selection was highlighted in chapter 6, with the emphasis on the elderly population. In the next decade not only the number of octo- and nonagenarians with gastric cancer will rise, but this group will also be more heterogeneous with respect to frailty. Reluctance towards extensive surgery in this age group still is high although some single centre studies show a favourable outcome. In this thesis we described outcome in a population based study of gastric cancer in octo- and nonagenarians in the North East part of the Netherlands in order to support decisions with regard to surgery. Although long term relative survival after surgery was comparable to the general population, the postoperative mortality was too high. Especially in the group 85 years and older, where one in three patients died within two months after surgery. We concluded that better selection procedures are required and improved peri-operative care is needed in order to reduce surgery related mortality.

As a consequence of better selection the group of octo- and nonagenarians not fit for surgery will rise. Appropriate studies in a palliatieve setting open to patients of this age group are rare, but with respect to our data are highly recommended so that the increasing demand for patient tailored therapy in this particular age group can be fulfilled. For the general population of patients with advanced gastric cancer many chemotherapeutic regimens have been explored but yet no standard treatment has evolved and prognosis is still grim. Various single- and combination chemotherapy regimens were tested in order to prolong survival, often at the expense of increased toxicity in case of combination therapy. We conducted a weekly dose escalation study of carboplatin, with epirubicin, leucovorin and 5-fluororouracil (CELF) and filgrastim in 12 patients with surgically incurable gastric cancer, described in chapter 7. This regimen, in an outpatient setting, proved feasible with an acceptable toxicity, and a response rate of 58% (95 % Confidence Interval (CI); 31-85 %). We therefore concluded that this might be a suitable regimen for further study. We also recommended performing late evaluations of studies, as our mature data showed an interesting and not expected long term symptom free

survival of two patients, of respectively 6 and 9 years after diagnosis. This could implicate that a subgroup of patients with a surgically incurable disease, not only will have palliative benefit, but may even find cure from chemotherapeutic interventions. In chapter 7a we presented a case history of a patient included in the CELF study described above, which illustrated how doctors could misinterpreted the effect of such an unexpected event as possible cure on patients. Although the medical team assumed that the patient would be relieved by being an exceptional long-term survivor, the opposite occurred. The patient reacted with a rare type of denial, namely retrospective denial of the diagnosis. This conviction was in accordance with the unexpected outcome and probably served well to reduce anxiety and uncertainty about recurrence of cancer; a pre-dominant preoccupation in most survivors of cancer. Most physicians are trained in guiding patients on their way to approaching death. However we concluded from this case history that for patients both negative as positive unexpected developments, in this case prolonged survival culminating in likely cure, requires intensive efforts in adaptation of care. In chapter 8 we reported data of a more recent phase II study of a 3- weekly chemotherapy regimen with oxaliplatin, leucovorin and Tegafur/Uracil (UFT) in a palliative setting. This two drug regimen showed a response rate of 35% (95% CI; 16-54%) and median overall survival of 8 months (95% CI; 4.5 – 11.5 months), which is comparable to other two drug regimens used in gastric cancer. The benefit of the current regimen however is the applicability in an outpatient setting with no hand foot syndrome problems, which develop in the majority of patients who are treated with capecitabine. For future studies with the new targeted agents, especially in the context of skin toxicity, a combination of such agents with UFT therefore seems to be superior in dealing with the hand foot syndrome.



Chapter 10

Nederlandse samenvatting

Nederlandse samenvatting

Maagkanker is wereldwijd nog steeds de vijfde meest voorkomende vorm van kanker en de tweede meest voorkomende oorzaak van sterfte ten gevolge van kanker. De persisterende hoge sterfte ten gevolge van deze ziekte wordt veroorzaakt door multipele factoren; die aan patiënt, tumor en behandeling gerelateerd zijn. In dit proefschrift werd de aandacht gevestigd op drie aspecten in relatie tot de overleving van maagkanker. Ten eerste, verschillen in patiënten karakteristieken die verschillen in diagnose, behandeling en uiteindelijk overleving zouden kunnen veroorzaken. Ten tweede, verschillen in ziekenhuisvariabelen die de overleving kunnen beïnvloeden. Ten derde, werden 2 hoofdstukken gewijd aan de meerderheid van de patiënten, diegenen met een vergevorderd stadium, die niet meer kunnen genezen, en aan hun behandelopties en de beperkingen daarvan.

In HOOFDSTUK 1 presenteerden we een overzicht van de perspectieven voor maagkanker ten aanzien van etiologie, diagnostische modaliteiten en behandelopties in curatieve en palliatieve setting. Het risico op het ontwikkelen van maagkanker wordt beschouwd als een interactie tussen een bacteriële risicofactor zoals Helicobacter Pylori en risico-factoren vanuit gastheer danwel omgeving.

Een genetische predispositie voor maagkanker is beschreven in families met atrofische gastritis, hereditair nonpolyposis colorectale kanker of in families die voldoen aan de criteria van erfelijk diffuus maagkanker (HDGC). Het risico gedurende het leven op het ontwikkelen van maagkanker in HDGC families, in patiënten met een *CDH1* mutatie is hoog en wordt geschat op ›80%.

In HOOFDSTUK 2 rapporteerden we de geno-/phenotypische data van alle 10 Nederlandse families met *CDH1* mutaties. We observeerden een variabele penetrantie van maagkanker tussen en binnen de Nederlandse families. De meeste dragers ondergingen een profylactische maagresectie, waarbij in de meeste gevallen multipele foci van intramucosaal carcinoom met diffuus verspreide zegelringcellen werden gezien, welke niet gedetecteerd waren bij screening. In families met CDH1 mutaties hebben vrouwen ook een verhoogd risico op het ontwikkelen van een lobulair mammacarcinoom (LBC). De incidentie van LBC was opmerkelijk laag in de Nederlandse families, in tegenstelling tot gegevens uit andere studies. Aangezien het de verwachting is dat door profylactische maagresecties de sterfte ten gevolge van maagkanker kan worden voorkomen, zal de incidentie van LBC waarschijnlijk toenemen. Mede gezien de moeilijkheid om LBC te detecteren bij screening adviseerden wij om een profylactische mastectomie

als optie ook te bespreken met *CDH1* mutatie draagsters. Ten slotte vonden wij een hoge incidentie van gespleten lip/gehemelte, dat de hypothese dat *CDH1* mutaties betrokken zijn bij verstoorde lip en gehemelte sluiting ondersteunt. Om de echte impact van deze observatie vast te stellen is verder onderzoek noodzakelijk in een groter patiënten cohort, om zo toekomstige ouders uit HDGC families raad te kunnen geven. Een hoog zoutgebruik, roken en een Helicobacter Pylori infectie zijn de meer algemeen erkende omgevingsrisicofactoren voor maagkanker, maar ook overgewicht en gastrooesophageale reflux komen veel voor. Het risico op het ontwikkelen van maagkanker is tevens verhoogd in patiënten met een lage socio-economische status (SES). In HOOFDSTUK 3 hebben we de invloed beschreven van SES op de overleving van maagkanker in de Noordoostelijke regio van Nederland. SES bleek een onafhankelijke prognostische factor voor overleving, met een lager risico op sterfte ten gevolge van maagkanker in de hoge SES groep. Bij patiënten die leefden in een hoge SES buurt werden meer resecties uitgevoerd en werd vaker chemotherapie toegediend. Daarbij werd in de lage SES groep de diagnose op oudere leeftijd vastgesteld. Desondanks bleken bij statistische analyse noch soort behandeling danwel leeftijd, geslacht, histologische gradering, tumor lokalisatie en stadium alleen, als enkelvoudige factoren, verantwoordelijk voor dit verschil in overleving. Duidelijk werd wel dat de onderlinge relatie tussen patiënt, tumor en behandeling factoren verrassend genoeg voldoende sterk was om het voordeel te niet te doen van distale kankers voornamelijk voorkomend in de lage SES groep, en het nadeel van hooggradige tumoren in de hoge SES groep.

Het doel van het Nederlandse gezondheidssysteem, financieel gebaseerd op een verplichte verzekeringsdekking, is om kwalitatief hoge medische zorg te verlenen en dit beschikbaar te maken voor alle inwoners. Echter verschillen in toegankelijkheid van medische zorg en de uitkomst hiervan kunnen ontstaan in groepen die op een of andere manier geïsoleerd zijn; sociaal, cultureel, religieus en/of communicatief. Om de gelijkheid danwel verschillen in het zorgsysteem te monitoren kan maagkanker dienen als een surrogaat marker, aangezien de uitkomst erg afhankelijk is van vroege detectie. In dit proefschrift, in HOOFDSTUK 4, analyseerden wij de overleving van een risicogroep voor het ontvangen van suboptimale zorg; eerste generatie niet westerse immigranten in de Noordoostelijke regio van Nederland. De uitkomst van maagkanker in deze groep bleek verrassend beter in vergelijking met westerse immigranten en autochtone patiënten, ook na correctie voor verstorende variabelen. Dit verschil kon niet direct worden verklaard, echter we konden concluderen dat

de toegankelijkheid van het gezondheidssysteem voor deze groep van immigranten niet leek belemmerd. We hypothetiseerden dat de sociale cohesie binnen de groep van immigranten en het typische Nederlandse dienstverleningssysteem voor werkgevers en werknemers ("de arbodienst") wellicht positieve bijdragende factoren waren. Factoren die noch patiënt noch tumor gerelateerd zijn kunnen ook bijdragen aan de uitkomst van in opzet curatieve chirurgie bij kanker patiënten.

Wat echter precies bijvoorbeeld de invloed van ziekenhuis volume en type en van de chirurgische ervaring op de uiteindelijke overleving is, is nog steeds niet geheel duidelijk. In HOOFDSTUK 5 rapporteerden wij de overlevingsdata van maagkanker in onze regio met betrekking tot ziekenhuis karakteristieken. Tussen de 15 niet opleidingsziekenhuizen, 8 opleidingsziekenhuizen en het enige academische centrum vonden wij geen invloed van opleidingsstatus danwel verwijsgedrag op de lange termijn overleving. Binnen de geringe variatie in aantal operaties per jaar in onze regio werden geen opvallende verschillen gevonden van ziekenhuis volume in relatie tot overleving. In univariant analyse leek de 5-jaars relatieve overleving van distale kankers beter in het academische ziekenhuis, echter dit werd niet bevestigd in multivariant analyse. Dit werd daarom wellicht verklaard door selectie bias, omdat gemiddeld genomen jongere patiënten werden geopereerd in het academische centrum.

Het onderwerp patiëntenselectie speelde een hoofdrol in HOOFDSTUK 6, waarbij de nadruk lag op de populatie ouderen. In het komend decennium stijgt niet alleen het aantal tachtig- en negentigjarigen met maagkanker, maar zal deze groep ook meer heterogeen zijn met betrekking tot frailty. Weerstand tegen uitgebreide operaties in deze leeftijdscategorie is nog steeds groot, hoewel sommige studies een gunstige overleving beschrijven.

In dit proefschrift hebben wij de overleving onderzocht onder tachtig- en negentigjarigen met maagkanker in Noordoost Nederland met als doel besluitvorming ten aanzien van operaties te ondersteunen. Hoewel de lange termijn relatieve overleving na een operatie vergelijkbaar was met de algemene populatie was de postoperatieve sterfte te hoog. Dit was vooral het geval in de groep 85 jaar en ouder, waar een op de drie patiënten overleed binnen twee maanden na de operatie. Wij concludeerden dat betere selectie procedures en betere perioperatieve zorg nodig is om sterfte ten gevolge van chirurgie te reduceren. Ten gevolge van betere selectie zal het aantal tachtig- en negentigjarigen die niet geschikt zijn voor chirurgie toenemen. Geschikte studies in een palliatieve setting die patiënten uit deze

leeftijdscategorie includeren zijn zeldzaam. Op grond van onze data is het sterk aan te bevelen dit onderzoeksgebied uit te breiden, om te kunnen voldoen aan de toenemende behoefte van patiënt gerichte behandeling in deze specifieke leeftijdsgroep.

Voor de algemene populatie van patiënten met een vergevorderd stadium van maagkanker zijn meerdere chemotherapeutische regiems onderzocht, maar tot op heden heeft dit niet geleid tot een standaard behandeling en de prognose is nog steeds somber. Verschillende enkele danwel combinatie chemotherapie regiems zijn getest met als doel de overleving te verbeteren, echter ten koste van toegenomen toxiciteit in het geval van combinatie therapie. Wij hebben een wekelijks dosis escalatie studie uitgevoerd van carboplatin met epirubicine, leucovorine en 5-fluorouracil (CELF) en filgrastim in 12 patiënten met chirurgisch incurabel maagkanker, beschreven in HOOFDSTUK 7. Dit regiem, in een poliklinische setting, bleek uitvoerbaar met een acceptabele toxiciteit, en een responsepercentage van 58% (95% betrouwbaarheidsinterval (CI); 31-85%). Wij concludeerden daarom dat dit wellicht een geschikt regiem was voor verder onderzoek. Tevens raadden we aan om late evaluaties van studies uit te voeren, aangezien onze mature data een interessante en niet verwachte lange termijn symptoomvrije overleving liet zien bij twee patiënten, respectievelijk 6 en 9 jaar na diagnose. Dit zou kunnen betekenen dat een subgroep van patiënten met chirurgisch incurabele ziekte, niet alleen in palliatief opzicht voordeel heeft van chemotherapeutische interventies maar dat wellicht ook genezing haalbaar is. In HOOFDSTUK 7A presenteerden wij de ziektegeschiedenis van een patiënt die geïncludeerd was in de CELF studie hierboven beschreven, welke illustreert hoe artsen het effect van een onverwachte gebeurtenis zoals mogelijk genezing voor een patiënt verkeerd konden interpreteren. Hoewel het medische team veronderstelde dat de patiënt opgelucht zou zijn door een uitzonderlijk lange overleving, gebeurde het omgekeerde. De patiënt reageerde met een vreemde vorm van ontkenning, namelijk retrospectieve ontkenning van diagnose. Deze overtuiging was in overeenstemming met de onverwachte uitkomst en kon waarschijnlijk goed de angst reduceren en de onzekerheid over terugkeer van kanker; een overheersende gedachte bij de meeste overlevenden van kanker. De meeste artsen zijn getraind in het begeleiden van patiënten op hun weg naar de dood. Echter wij concludeerden van deze casus dat voor patiënten zowel negatieve als positieve onverwachte ontwikkelingen, in dit geval toegenomen overleving waarschijnlijk resulterend in genezing, intensieve aandacht vereist in aanpassing van zorg. In HOOFDSTUK 8 rapporteerden wij de data van een meer

recente fase II studie van een 3 wekelijkse chemotherapie regiem met oxaliplatine, leucovorine en Tegafur/Uracil (UFT) in een palliatieve setting. Dit twee drug regiem toonde een response rate van 35% (95% CI; 16-54%) en een mediane overall overleving van 8 maanden (95% CI; 4.5-11.5 maanden), welke vergelijkbaar zijn met andere twee drug regiems die gebruikt worden bij maagkanker. Het voordeel van het huidige regiem echter is de toepasbaarheid in een poliklinische setting zonder handvoet syndroom problemen, welke zich voordoen bij de meerderheid van de patiënten die behandeld worden met capecitabine. Voor toekomstige studies met de nieuwe doelgerichte middelen, vooral in de context van huidtoxiciteit, lijkt daarom een combinatie van zulke middelen met UFT superieur om te kunnen omgaan met het handvoet syndroom.

Dankwoord

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